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HEART RATE, PR INTERVAL AND STROKE VOLUME RESPONSE TO EXERCISE IN PACED AND NON-PACED SUBJECTS

BY

MARGARET ANNE REES (C)

A THESIS

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The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled HEART RATE, PR INTERVAL AND STROKE VOLUME RESPONSE TO EXERCISE IN PACED AND NON-PACED SUBJECTS submitted by Margaret Anne Rees in partial fulfilment of the requirements for the degree of Master of Science in Physical Education and Sport Studies.

Supervisor

DATE : September 25, 1989

DEDICATION

To Charlotte

A true friend who supported me through the joys and sorrows.

To Misty

For her unquestioning love.

ABSTRACT

Dual chambered pacing is utilized in the treatment of symptomatic bradycardia resulting from atrioventricular (AV) block. These pacemakers allow rate responsiveness along with AV synchrony, both of which can augment cardiac output. At present the AV delay, representing the timing of the atrial contraction relative to the ventricular contraction, is fixed at some programmed value. It has been suggested that there is a need to adjust this AV delay relative to the pacing rate.

This investigation was completed in 2 stages. First, an inverse relationship between heart rate (HR) and PR interval was confirmed in two groups of normal subjects and a group of post myocardial infarction (MI) patients undergoing a standardized exercise test. This relationship was then utilized to assess the timing of atrioventricular (AV) synchrony in atrial tracking pacemakers for increasing stroke volume during exercise.

Eight subjects (61 $\pm$ 3.4 years) with complete heart block paced in the atrial tracking mode performed exercise testing on a bicycle ergometer. Heart rate (HR), stroke volume (SV), blood pressure (BP), cardiac output (CO) and Borg Scale values obtained during exercise. At matched heart rates, a rate adapting AV delay was compared to a constant delay of 200 msec. CO was measured non-invasively via Impedance Cardiography (IC). An initial test was performed to determine HR response; this information was used in a second exercise test to program the

relative AV delay

The results of Test 1 showed an abnormal pattern of SV response in 7 subjects.

Results of Test 2 showed no significant differences ($p<0.05$) in the measured parameters between a constant 200 msec. and a rate adapting AV delay.

These results suggest that this group of subjects have a variable SV response to exercise. A rate adapting AV delay based on the normal relationship had no significant effect upon stroke volume during exercise when compared to a constant delay of 200 msec. It appears that the ability to increase HR is the key factor for raising CO during exercise performance.

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CHAPTER 1

INTRODUCTION

In Sweden in 1958, Elmquist and Senning implanted a pacemaker in a human for the first time in history (2). Permanent cardiac pacing is instituted to treat derangements or deficiencies of the heart's conduction system, a treatment aimed at avoiding a life-threatening loss of cardiac output. Early pacemakers provided an unsynchronized stimulus to the atria or ventricles alone, ensuring survival. Since then there have been many technological advances resulting in increased complexity and reliability of pacemaker units, power sources and lead systems. This diversity of equipment has extended the emphasis from pure survival to a desire to restore normal function. In the forefront is the need to adequately meet the metabolic demands of daily activity.

Fully automatic pacemakers allow multiprogramability, having the ability to sense and pace in both the atria and ventricle with a variety of programable atrioventricular (AV) intervals. In the atrial tracking mode, these units allow restoration of two key factors in normal hemodynamics; rate responsiveness and AV synchrony. Rate responsiveness allows for acceleration of the ventricular pacing rate; the pacemaker unit senses the increased intrinsic sino-atrial activation by "tracking" the atrium and then paces the ventricle at the increased rate. This is a definate advantage over fixed rate pacing where the atrial

rate can increase but the ventricle is fixed at a rate such as 70 beats·min^{-1} (3).

Synchronous pacing ensures that the contractions of the atria and ventricles occur in the appropriate sequence, with subsequent enhancement of cardiac output (2,3,5). At present, the timing interval or atrioventricular (AV) delay between the atrial and ventricular contraction remains constant once programmmed. It has been shown that a constant AV delay can result in the loss of AV synchrony with increasing heart rates (5). In non-paced subjects increased heart rates are associated with more rapid conduction (6), resulting in a shorter delay between atrial and ventricular contraction. There is a need to document this relationship if it is to be used in the programming of pacemakers. Adjusting the AV delay relative to the increase in heart rate in atrial tracking pacing would ensure a properly-timed atrial systole relative to ventricular contraction. This may result in an increased stroke volume and cardiac output during exercise.

The future challenge in providing optimal hemodynamics may be to design a pacemaker unit which incorporates an algorhythm adjusting the AV delay relative to the pacing rate.

Hypotheses to be Tested

1. Can heart rate - PR interval profiles be generated for normal subjects as well as post myocardial infarction patients?

2. Is the heart rate - PR interval relationship the same in normal subjects and post myocardial infarction patients?

3. Is there a linear relationship between heart rate and PR interval in normal subjects and post myocardial infarction patients?

4. Can a rate adapting AV delay for use in pacemakers can be based upon this relationship?

4. Can stroke volume - heart rate profiles during exercise can be generated in subjects with atrial tracking pacemakers by impedance cardiography?

5. Are stroke volume and cardiac output during exercise in subjects with atrial tracking pacemakers greater utilizing a rate adapting AV delay than a constant AV delay of 200 milliseconds?

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CHAPTER 2

GENERAL METHODS

Measurement of Stroke Volume and Cardiac Output

Impedance cardiography involves the transmission of a high frequency current across the chest. As this sinusoidal current is passed across a cylindrical fluid system, the ejection of a given volume into the cylinder will cause an impedance wave. The area of this wave will be directly proportional to the increase in volume.

Teo et al (5) assessed the measurement of cardiac output via impedance cardiography versus the direct Fick method in patients with coronary artery disease. There was less than 5% random error and no significant systematic error obtained at rest and two stages of steady state exercise. The authors also tested normal subjects one week apart, finding results that were highly reproducible.

Goldstein et al (3) compared non-invasive impedance cardiography with the invasive thermodilution method under various manipulations including cardiac pacing. The correlation between stroke volumes measured by the two methods was 0.97 for pacing at baseline, 130 and 150 beats $\cdot$ min^{-1}.

The Minnesota Impedance Cardiograph Model 304B (Surcom Inc., Minneapolis) was used in this study to measure cardiac output. In this non-invasive technique, four self-adhesive mylar backed electrode bands were placed around the neck and chest prior to

exercise testing. The two electrodes around the neck were placed 3 - 5 cm. apart. A third was around the chest at the level of the xiphisternum, with the forth at least 5 cm. below the third band. A microphone to record heart sounds was held over the precordium via an elastic strap.

When connected to the impedance cardiograph a weak current is passed through the outer two electrodes and sensed by the inner electrodes. Mean total impedance (Zo) between the inner electrodes is computed and displayed on the unit. A four channel ink recorder (Model 8188 Gould Inc., Cleveland at the Walter C. MacKenzie Centre and Model 7404A Hewlett Packard Inc. at the Central and Northern Alberta Cardiac Rehabilitation Centre) provided simultaneous recordings of the electrocardiogram, the phonocardiogram, mean impedance changes (Zo) and rate of impedance change (dZ/dt) for each cardiac cycle. Left ventricular ejection time (LVET) and dZ/dt_{min} were determined from the recordings (see Figure) with the average of 5 cardiac cycles being utilized. Calculation of stroke volume was made using the following equation (4):

$$\text{Stroke Volume} = \frac{P \times L^2 \times LVET \times dZ/dt_{min}}{Zo^2}$$

P = the resistivity of blood at body temperature where $P = 53.2e^{0.022H}$

H = hematocrit (%).

L = the average length between the inner electrodes measured at the anterior and posterior midline (centimeters).

LVET = left ventricular ejection time (seconds).

dZ/dt_{min} = the minimum value for the rate of change in impedance during the cardiac cycle (ohms·second^{-1}).

Zo = the mean total impedance between the inner electrodes (ohms)

Measurements were made at rest and during exercise with the subjects seated upright upon the bicycle ergometer. In order to reduce artifact on the recordings the subjects were asked to stop all movement and breathhold at normal end-exhalation. When cycling this required the subject to stop pedalling for 5 - 10 seconds while 8 - 10 heartbeats were recorded at the end of each exercise stage. A blood sample for hematocrit was obtained from the antecubital vein immediately following completion of the protocol.

Stroke volume was calculated as outlined above, heart rate was determined from the simultaneous electrocardiogram recording and cardiac output calculated as the product of heart rate and stroke volume.

Methodological Considerations

Goldstein et al. (3) noted distortion of dZ/dt waveforms during cardiac pacing resulting in bifid peaks or pre-systolic peaks and valleys. They suggested that these deviations could affect the measurement of the tracing. However, agreement with the thermodilution technique was still obtained in their study.

During the present study, it was noted that the onset of

ejection on the dZ/dt tracing did not always have a clearly definable point. Rather than the usual rapid change in the waveform, a more gradual change was recorded making the marking of the onset point more difficult. The following marking criteria were used for measuring LVET:

1. The onset point must fall at or after the completion of the QRS complex.
2. The onset point must be within the latter part of the first heart sound.
3. The onset point as so defined must represent a consistent deflection in the dZ/dt waveform.
4. The endpoint must coincide with the first major deflection of the second heart sound, in the area of the X point of the dZ/dt waveform.

These marking criteria were assessed in comparision to the ejection times obtained using carotid pulse tracings in five subjects with fully automatic pacemakers. Simultaneous recordings of impedance cardiography and the carotid pulse wave were made at rest and following one 5 minute stage of exercise. Three to five cardiac cycles were analyzed for LVET, then averaged. At rest in the upright seated position there was total agreement between the two measures; 0.265 ± 0.010 sec. for the carotid pulse tracing and 0.265 ± 0.010 sec. for the impedance tracing at a heart rate of 65 ± 1.3 beats$\cdot$min^{-1}.

After light exercise, there was significant difference ($p<0.05$) between the two measures. LVET assessed by carotid

pulse was 0.250 ± 0.011 sec. and 0.228 ± 0.004 sec. by impedance cardiography at a heart rate of 78 ± 2.4 beats·min^{-1}. An alternative method of marking the impedance waveform was utilized. The first major deflection of the dZ/dt tracing from baseline was identified as the onset point. At 0.267 ± 0.012 sec., this also proved to be significantly different ($p<0.05$) from the carotid tracing. This marking resulted in several cases where the onset point occurred prior to the first heart sound.

The original marking criteria were used throughout the study despite systematically underestimating the LVET as measured by carotid pulse tracings. This could result in a 4-10% difference in the calculated stroke volumes. Despite this, it was felt that impedance cardiography provided a simple, inexpensive method to obtain sequential measurements during a progressive exercise test.

Measurement of PR Intervals

Electrocardiograms were recorded in association with impedance cardiography. A 5 - 10 second recording was taken at rest and at the end of each exercise stage. A paper speed of 50 mm/sec. was utilized. The subject was asked to stop all movement and breath hold at end exhalation for the recording period to reduce artifact.

The PR interval was measured as the first deflection from baseline of the P wave to the first deflection of the QPS

complex (2). The intervals were hand measured by a single observer using calipers. A random error of 5% was found on a test-retest assessment. Five to 8 individual heart beats were averaged and nearest 10 msec. value was utilized.

Pacemaker Reprogramming

Pacemaker reprogramming requires the use of an external unit that provides the programming instructions. Prior to the actual reprogramming, specific information such as pacing mode, sensitivity, upper rate limit, lower rate limit and AV delay must be selected from the programming choices. Once programmed, the unit is held in place over the implanted pacemaker. A magnet acts to blank out the existing information and replaces it with the new program. Only the information that is to be changed is affected. There is virtually no delay when reprogramming and the patient does not suffer from any loss of pacemaker stimulus.

As programming units are specific to the pacemaker, two units were used in this study. A Medtronic Model 9710 programmer (Medtronic Inc.,Minneapolis) and a Cordis Programmer 3 Model 255A (Cordis Corp.,Miami). Pacemakers were reprogrammed immediately after the taking of impedance cardiography measurements.

Blood Pressure and Borg Scale

Blood pressure was assessed via auscultation using a mercury sphygmomanometer. Measurements were taken during the last minute of each exercise stage.

During the last 30 seconds of each stage the subject was asked to give a rating of perceived exertion using the Borg Scale. (1)

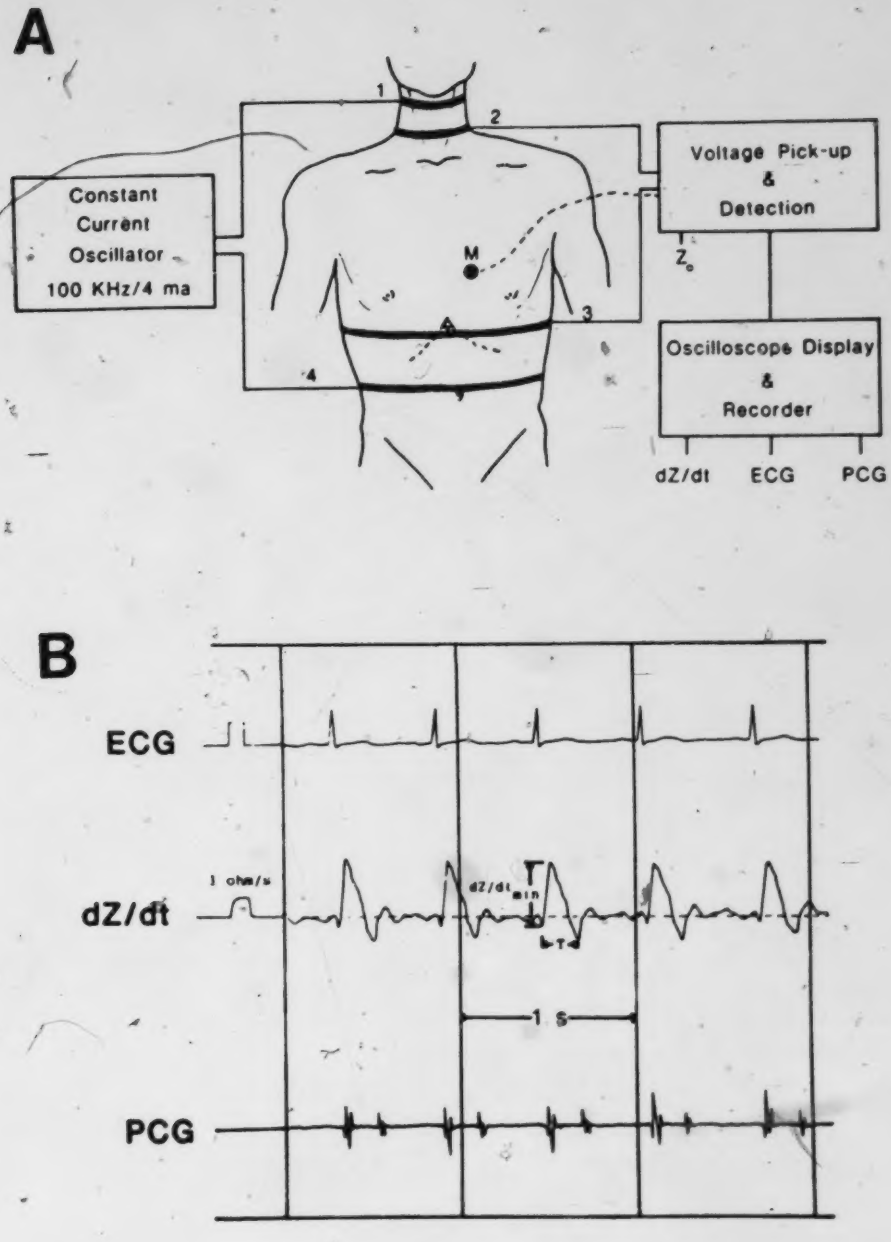

Figure 2.1: A) Electrode placement for impedance cardiography.
B) A typical impedance cardiograph recording.

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CHAPTER 3

HEART RATE - PR INTERVAL RELATIONSHIP

INTRODUCTION

The PR interval is that portion of the electrocardiogram which immediately follows sinoatrial node activation. This interval contains the electrical events of atrial depolarization and conduction of the electrical impulse through the atrioventricular node, Bundle of His, bundle branches and Purkinje fibres to the ventricular muscle. Normal resting duration of the PR interval is 160 - 200 milliseconds (msec)(8).

The decrease in the PR interval associated with the increased heart rate of exercise has been acknowledged (7,17). Still, the precise relationship has not been extensively documented.

Simmoons and Hugenholtz (17) provided a description of the conduction interval shortening from rest to maximal exercise through the analysis of standard electrocardiograms from healthy men. The peak of the P wave to the start of the QRS complex was utilized instead of the customary PR interval. The authors found a linear relationship between peak P-Q interval and heart rate representing a relative change of 3.6 msec/10 beats in heart rate.

Invasive methods were used by Daubert et al (7) to assess the relationship between PR interval and heart rate in healthy subjects. Catheter electrodes were used to sense the intrinsic

electrical activity. It was observed that the PR interval variation was inversely proportional to the spontaneous heart rate increase induced by exercise, with a change of 4.0 $\pm$ 2 msec/10 beats. Linear correlations on individual data were significant (r values between 0.73 and 0.97).

The purpose of this study was to confirm this relationship between the PR interval and heart rate in 2 groups of normal, healthy subjects as well as in a group of post-myocardial infarction patients. Stroke volume, cardiac output and blood pressure were measured to observe any deviation from the expected response.

METHODS

Subjects

Three groups of 16 subjects were studied (see Table 3.1 for Physical Characteristics). Group A consisted of young healthy, trained males, 30 years of age and under. Group B was made up of healthy, untrained males, over 30 years of age. Group C contained patients diagnosed as having a prior myocardial infarction (MI). The site of infarction was determined by electrocardiogram, half the group was diagnosed with an anterior infarct and the other half with an inferior infarct.

All subjects gave signed consent prior to exercise testing. Normal subjects also completed a pre-test questionaire on health status and activity patterns. Patients were tested as part of a routine follow-up after infarction. Any prescribed medications

were continued during the time of the study; none of the patients were taking beta blockers.

Groups A and B were tested in the Department of Cardiology at the Walter C. MacKenzie Health Sciences Centre. Group C performed exercise testing at the Central and Northern Alberta Cardiac Rehabilitation Centre.

Exercise Protocols

Exercise protocols were varied to match the specific work capabilities of the different groups. All subjects were exercised in the upright postion on a electrically braked bicycle ergometer; a Seimens Model EM740 at Walter C. MacKenzie Centre and a Seimens Model EM840 at the Central and Northern Alberta Rehabilitation Centre. Stroke volume was measured at rest and at the end of each stage via impedance cardiography. Electrocardiograms for PR analysis were recorded in association with impedance cardiography measurements; a modified V5 lead system was used. Blood pressure was recorded at the beginning of the last minute of each exercise stage using a mercury sphygmomanometer. In Group A, blood pressure was not measured after a power output of 250 watts.

Group A : Power output was initially set at 100 watts and increased by 50 watts every 2 minutes until the subject reached a plateau or decrease in VO_2.

Group B : The power output was initially set at 30 watts and

increased sequentially to 50, 80, 130, 180 and 230 watts every 3 minutes until the subject reached exhaustion (Borg scale reading greater than 18) or attained 95% of their age predicted maximum heart rate.

Group C : The initial power output was 30 watts with an increase of 20 watts every 3 minutes until the patient reached 85% of their age predicted maximum or presented with symptoms that were indications for stopping as outlined by the American College of Sports Medicine (1).

Measurement of PR Intervals

Electrocardiograms were recorded at a speed of 50 mm/sec. A 10 second recording was taken at the end of each exercise stage in association with the impedance cardiography measurement of stroke volume. The subject was asked to stop cycling and breath hold at end exhalation for the recording period to reduce the motion artifact. PR intervals were measured by hand using calipers. The PR interval was defined as the first deflection from baseline of the P wave to the first deflection of the QRS complex (4). Measurements were rounded up or down to the nearest 10 msec. Recorded values were averaged over a range of 5-8 heart beats. Heart rate was determined from these same beats.

Statistical Analysis

All group data were expressed as the mean ± standard error of the mean (SEM). Least squares regression analysis comparing heart rate and PR interval was assessed for each group. An analysis of covariance was used to estimate the difference between groups for change of PR interval relative to heart rate. A p valve of <0.05 was taken as the level of significance.

RESULTS

A total of 48 male subjects were studied in three separate groups. Group characteristics are presented in Table 1. The mean age of Group A (younger healthy) was 25 ± 1 years, Group B (older healthy) was 39 ± 2 years and Group C (post MI patients) was 51 ± 2 years.

Table 3.1

Physical Characteristics of Normal and Post MI Subjects

Group	N	Age (years)	Height (cm)	Weight (kg)
A	16	25 ± 1	178.5 ± 1.8	76.6 ± 1.8
B	16	39 ± 2	175.0 ± 1.0	78.2 ± 2.4
C *	16	51 ± 2	176.3 ± 1.1	88.9 ± 2.1

Mean ± SEM
* Anterior MI n=8, Inferior MI n=8

All groups showed similar mean resting heart rates and PR

intervals (see Table 3.2). Two individuals in Group A presented with resting PR intervals of 220 and 210 msec. No other deviations from the normally accepted range were observed. The two normal groups were able to exercise to higher intensities; the younger group reaching an average of 94 % of their mean age predicted maximal heart rate and the older group reaching 93 % of their mean value. The patient group was able to attain 80 % of the mean age predicted maximal heart rate. All subjects showed a decrease in PR interval when heart rate increased in response to exercise. The higher attainable heart rates coincided with a greater decrease in PR interval.

Table 3.2

Heart Rates and PR Intervals at Rest and Peak Exercise for Normal and Post MI Subjects

Group	Heart Rate (beats·min^{-1})			PR Interval (msec)		
	Rest	Peak	Change	Rest	Peak	Change
A	73 ±4	184 ±2	111 ±4	164 ±6	107 ±4	58 ±6
B	69 ±2	167 ±4	97 ±4	163 ±4	116 ±3	47 ±4
C	70 ±2	136 * ±4	66 ±4	164 ±4	137 ±4	28 ±3

mean ± SEM
* 85% Of age predicted or symptom limited maximum

A negative linear relationship between heart rate and PR interval was confirmed for each group (see Figure 3.1).

Regression equations are detailed in Table 3.3. Correlation coefficients were 0.73, 0.77 and 0.49 for Groups A, B and C, respectively. The r value for the pooled data (Group A+B+C) was 0.71. All correlations proved to be significant ($p<0.05$).

As the subjects progressed from rest to peak exercise, Group A showed an average decrease in PR interval of 58 $\pm$ 7 msec. while heart rate increased an average of 111 $\pm$ 4 beats$\cdot$min^{-1}.

Table 3.3

Regression Analysis for Prediction of PR Interval for Normal and Post MI Subjects

Group	Regression Equation	r
A	y = - 0.49 x + 201.30	0.73 *
B	y = - 0.45 x + 195.13	0.77 *
C	y = - 0.35 x + 185.82	0.49 *
A+B+C (Pooled)	y = - 0.45 x + 194.80	0.71 *

* Significant $p<0.05$

This represents a relative change of 5.2 msec/ 10 beats. Group B had a relative change of 4.9 msec/10 beats as PR interval decreased 47 $\pm$ 4 msec and heart rate increased 97 $\pm$ 3 beats$\cdot$min^{-1}.In Group C, PR interval decreased 28 $\pm$ 3 msec and heart rate increased 66 $\pm$ 4 beats$\cdot$min^{-1} for a relative change of 4.2 msec/10 beats. The relative change for each group was compared to the information of Daubert in Table 3.4.

In addition, peak P wave to QRS complex intervals were measured for Group B for comparison with the information from Simmoons and Hugenholtz. The relative change from rest to maximal exercise was 3.4 msec/10 beats.

The 2 individuals in Group A with longer than normal resting PR intervals showed a relative change from rest to maximum exercise of 9.6 and 9.4 msec/10 beats, much greater than the mean of the remainder of the group, 4.6 msec/10 beats.

Table 3.4

Comparison of Relative Change in PR/10 beats and Peak P-QRS/10 beats

	PR/10 beats (msec)	PKP-QRS/10 beats (msec)
Group A	5.2	
Group B	4.9	3.4
Group C	4.2	
Daubert et al	4.0	
Simmoons & Hugenholtz		3.6

Two subgroups were examined for age influences in the normal groups. The observed relative change was 4.9 msec/10 beats for a subgroup of Group A; mean age 22 $\pm$ 1 years, N = 8. A change of 4.9 msec/10 beats was also observed for Group B subjects greater than 40 years of age (mean 47 $\pm$ 1 years, N = 7).

An analysis of covariance was performed on the slopes and elevations of the linear regressions (see Table 3.5). There proved to be no significant differences between the 3 groups.

Cardiac output was similar at rest in the two normal groups; 6.1 $\pm$ 0.2 $l \cdot min^{-1}$ for Group A, 4.8 $\pm$ 0.1 $l \cdot min^{-1}$ for Group B (see Table 3.6). In Group C, this was somewhat lesser at 4.1 $\pm$ 0.3 $l \cdot min^{-1}$. All three groups progressively increased cardiac output from rest to maximum exercise (Figure 3.2). Group A were able to achieve the highest exercise cardiac

output of 21.9 ± 0.5 $l \cdot min^{-1}$ at a power output of 352 ± 10 watts. Group B had a cardiac output of 16.9 ± 0.3 $l \cdot min^{-1}$ at 214 ± 6 watts, accounted for by a lower peak heart rate and a smaller maximum stroke volume.

Table 3.5

Analysis of Covariance for the Heart Rate - PR Interval Relationship in Normal and Post MI Subjects

Group	Slope			Elevation		
	F	df	Decision	F	df	Decision
A = B	0.395	1,186	NS	0.374	1,187	NS
A = C	2.664	1,186	NS	0.039	1,187	NS
B = C	1.792	1,186	NS	0.105	1,187	NS

NS = Not Significant, $p<0.05$Table 3.6

Group C had a peak exercise cardiac output of 11.6 ± 0.9 $l \cdot min^{-1}$ at a power output of 120 ± 3 watts under a symptom limited protocol.

Stroke volume in all three groups increased during exercise to maximum values near 120 beats $\cdot min^{-1}$ (Figure 3.3). Despite a similar pattern of response, resting and exercise stroke volumes varied between groups. Resting values were 87 ± 5 $ml \cdot beat^{-1}$ for Group A, 70 ± 2 for Group B and 58 ± 4 for Group C. Group A was able to achieve the greatest maximum exercise stroke volume of 119 ± 3 $ml \cdot beat^{-1}$, Group B with 102 ± 2 $ml \cdot beat^{-1}$ and then Group C at 86 ± 6 $ml \cdot beat^{-1}$. The post MI patients, Group C, had a 7% decrease in stroke volume at peak exercise from the previous workload.

Systolic and diastolic blood pressure followed the

expected pattern of response in all 3 groups (Figure 3.4). There was a gradual rise in systolic pressure, while diastolic pressures remained virtually unchanged. Thus, mean arterial pressure rose gradually from rest to peak exercise (Figure 3.5).

Hemodynamic Values During Exercise Testing in Normal and Post MI Subjects

PO (watts)	HR ($b \cdot m^{-1}$)	SV ($ml \cdot m^{-1}$)	CO ($l \cdot m^{-1}$)	MAP (mmHg)
Group A				
Rest	72 ± 4	87 ± 5	6.1 ± 0.2	95 ± 2
100	105 ± 4	110 ± 4	11.1 ± 0.3	99 ± 2
150	123 ± 4	116 ± 5	13.7 ± 0.4	106 ± 2
200	145 ± 3	115 ± 5	16.3 ± 0.5	110 ± 2
250	162 ± 3	117 ± 5	18.6 ± 0.4	113 ± 2
MAX	184 ± 2	119 ± 3	21.9 ± 0.5	N/A
Group B				
Rest	69 ± 1	70 ± 2	4.6 ± 0.1	91 ± 2
30	82 ± 2	79 ± 3	5.6 ± 0.2	97 ± 2
50	89 ± 2	86 ± 3	7.0 ± 0.2	100 ± 1
80	104 ± 2	94 ± 3	9.0 ± 0.3	103 ± 1
130	126 ± 3	102 ± 2	12.8 ± 0.3	108 ± 1
PEAK	167 ± 4	102 ± 2	16.9 ± 0.3	120 ± 2
Group C				
Rest	70 ± 2	58 ± 4	4.1 ± 0.3	88 ± 2
30	80 ± 3	76 ± 5	6.0 ± 0.4	96 ± 3
50	90 ± 3	81 ± 4	7.2 ± 0.4	96 ± 3
70	102 ± 3	88 ± 5	9.1 ± 0.6	101 ± 3
90	117 ± 3	92 ± 6	10.7 ± 0.8	106 ± 3
PEAK	136 ± 4	86 ± 6	11.6 ± 0.9	110 ± 3

PO = Power Output
HR = Heart Rate
SV = Stroke Volume
CO = Cardiac Output
MAP = Mean Arterial Pressure

Group A: MAX PO = 352 ± 10 watts
Group B: PEAK PO = 214 ± 6 watts
Group C: PEAK PO = 120 ± 3 watts

Discussion

The purpose of this study was to explore the relationship between heart rate and PR interval during exercise in different subject groups. The groups were chosen to represent specific physical capabilities, looking for variation due to physical training status, age and health status.

An important consideration is that of the methodology used in the determination of PR intervals. The intervals were measured by hand from ECG tracings obtained at the end of each exercise increment. Daubert et al (7) measured intervals during right heart catheterization. In this study, non-invasive monitoring was chosen for the obvious simplicity and lower risk to the subjects.

A negative linear relationship between heart rate and PR interval was observed in the three different groups. This agrees with the findings of other authors (7,17). Lister et al (13) showed that AV conduction time was influenced by the same neuro-humoral stimuli that effect heart rate. The decreased vagal tone and increased sympathetic drive associated with exercise increases heart rate and speeds AV conduction.

Well conditioned athletes have been known to present with high vagal tone evident in bradycardia and prolonged AV conduction (3). This was observed in two subjects in Group A. The PR interval was longer than the normally accepted range and

bradycardia was evident at rest. With the onset of exercise the heart rate increased and PR interval decreased following the same pattern as the rest of the group, but with the relative change being much greater. These 2 individuals were also able to achieve higher maximum heart rates and shorter PR intervals than the group mean. It is interesting to note that this phenomena was not seen in all the members of the trained group; the literature cites this occurring in some but not all trained individuals (3,9,12), presumably due to the individual variation in autonomic tone.

It has been observed that there is a slight but significant increase in PR interval with increasing age. Simonsen (18) cites a 10 msec. increase in resting PR interval from the third to sixth decade. This lengthening of the PR interval or slowing of conduction time would produce a decrease in the relative change in PR interval/10 beats·min^{-1}. It may be that the decline in relative change with increasing age is another result of the alterations in the autonomic nervous system observed with aging (15). It is readily accepted that maximum heart rate decreases with aging due to this process. In the present study the relative change decreased from 5.2 msec. in Group A (mean age 25 years) to 4.9 msec. in Group B (mean age 39 years) to 4.2 msec. in Group C (mean age 51 years).

When subgroups of the 2 normal groups were assessed a decreasing trend was not evident; Subgroup A (mean age 22 $\pm$ 1 years) and Subgroup B (mean age 47 $\pm$ 1 years) both presented

with a relative change of 4.9 msec/ 10 bpm. The lack of large sample numbers may preclude any firm conclusions.

All three groups showed a pattern of cardiac output, stroke volume and blood pressure response consistant with the literature (2,10). The groups did have expected variations due to their characteristics. The younger, trained group was able to exercise to a higher intensity, attaining higher stroke volumes and heart rates for a greater cardiac output. Mean arterial blood pressure was lower than in the older groups at any comparable power output. The untrained, older group achieved lower maximal heart rates, stroke volumes, and cardiac output. As well, this group achieved a lower exercise maximum power output. The patient group had a further attenuated response to exercise associated with the symptom limited nature of testing. Higher mean arterial blood pressures seen in the 2 older groups could be attributed to the effects of aging upon afterload parameters.

Aging has been shown to produce decreased stroke volumes due to the effects on preload, afterload and contractility. Increased stiffness of the ventricle resulting in a lower compliance and filling, increased aortic stiffness producing higher mean and systolic pressures as well as a lessened response to inotropic agents are major factors involved (15,19). In addition, myocardial infarction can produce variable stroke volume and blood pressure responses due to the effects of underlying disease, extent of myocardial damage and the

efficiency of residual function and neurohumoral adjustments to exercise (10).

The reason for the close relationship between heart rate and PR interval may be linked to the need for optimal timing of atrial and ventricular contractions in ensuring optimal stroke volume. An appropriately timed atrial systole is known to enhance preload and following the Frank-Starling mechanism, increase stroke volume. In addition to increased ventricular filling, atrial systole assists in the closure of the AV valves (4,6). Without their closure blood could regurgitate into the atria when the ventricles contract, resulting in a decrease in effective stroke volume.

Brockman (5) noted maximum hemodynamic values in dogs with surgically induced complete heart block when spontaneous PR intervals were in the range of 85-125 msec. Stroke volume increased up to 27 ml.,end diastolic fibre length increased up to 40% and aortic pressure increased up to 25 mm Hg. with optimal intervals. Values were lessened at intervals that were either longer or shorter. Samet, Bernstein and Levine (16) recorded peak end diastolic pressures with a normal temporal sequence between the P wave and QRS complex in patients with complete heart block. They felt this demonstrated the augmenting of ventricular filling by atrial systole.

When the PR interval was held at a constant valve of 60-80 msec. in artificially paced dogs with induced heart block, Mitchell et al (14) found that stroke volume declined as heart

rate increased. The loss of AV synchrony produced a greater decrease in stroke volume with higher heart rates.

Leman and Kratz (11) observed the effects of various AV delays in subjects implanted with dual chamber pacemakers. When heart rate was increased in response to exercise there was an increase in end diastolic volume ratio and stroke volume ratio with a shorter AV delay.

Relating the normal sequence of the electrocardiogram to physiological events in the heart substantiates the need for the change in PR interval relative to the change in heart rate. The P wave denotes atrial depolarization, onset of ventricular systole and AV valve closure coincides with the end of the QRS and AV valve reopening occurs after the T wave. If the PR interval is too short, atrial contraction could occur against AV valves closed with the onset of ventricular systole. With inadequate time for atrial emptying, a portion of the atrial contribution to ventricular filling would be lost. If the atrial contraction precedes the QRS by too long an interval, the atria will be relaxed by the time ventricular systole occurs and blood could regurgitate through the AV valves. If the PR interval is extremely long the P wave will start encroaching upon the preceding T wave and atrial contraction could occur against valves still closed from the previous ventricular contraction.

In conclusion, a linear relationship between heart rate and PR interval has been confirmed in three different groups.

The reason for this may lie in the need to ensure the synchrony of atrial and ventricular contractions in maintaining optimal stroke volume during increasing demands for cardiac output.

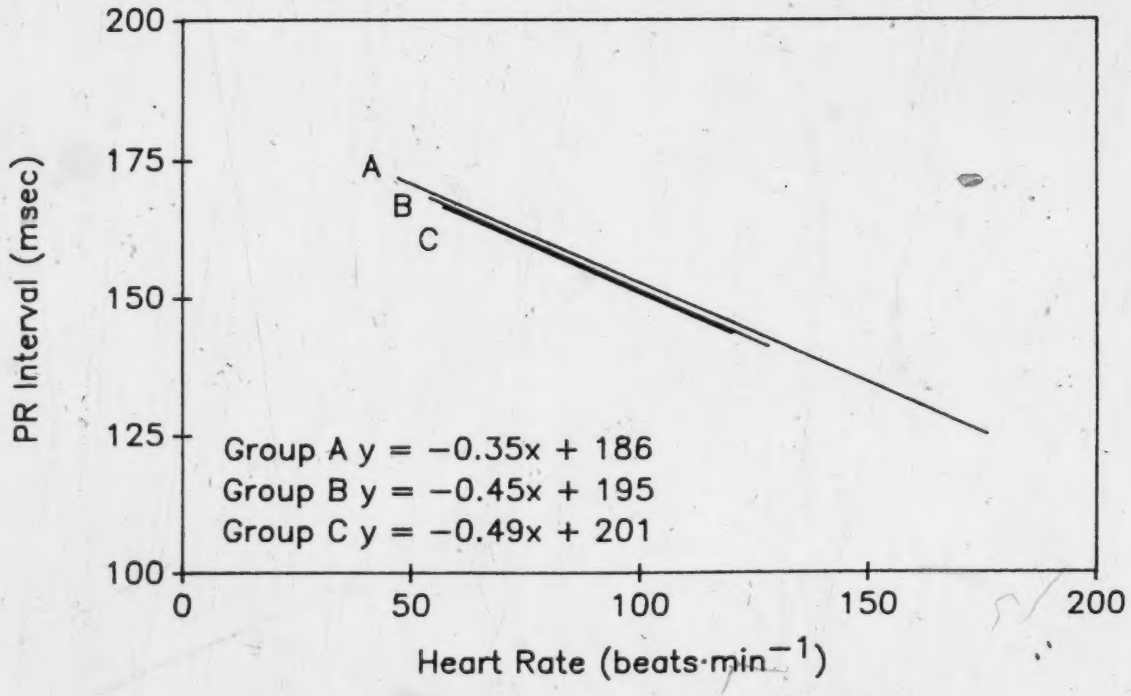

Figure 3.1 : Linear Regression of PR Interval and Heart Rate from Electrocardiogram for Young Normal (Group A), Older Normal (Group B) and Post Myocardial Infarction (Group C) Subjects.

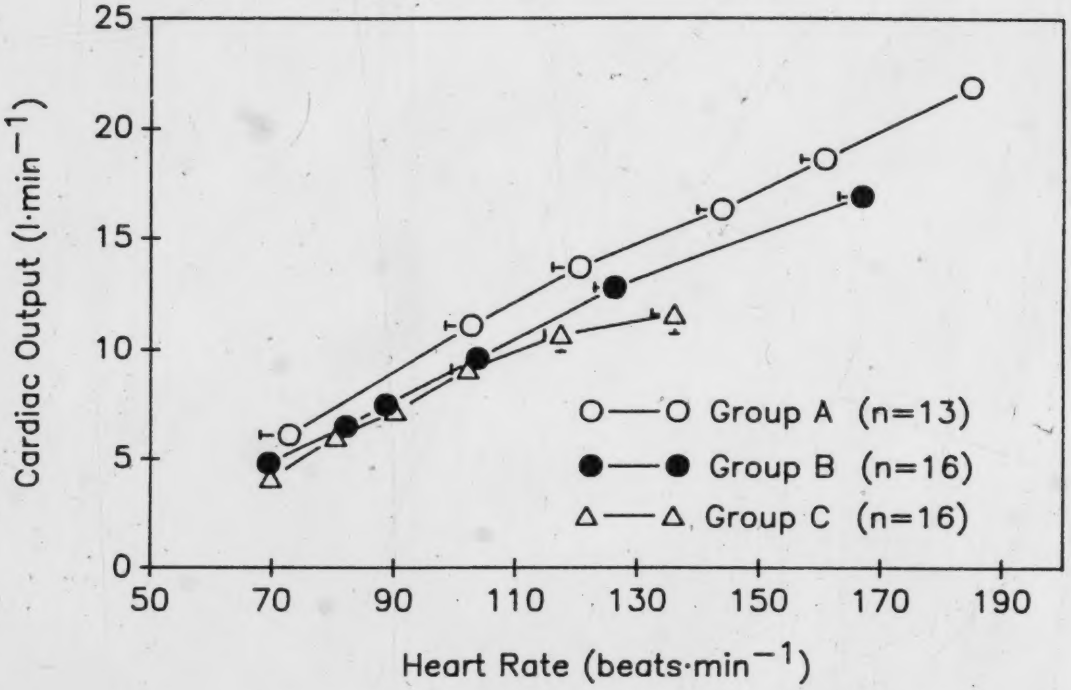

Figure 3.2 : Changes in Cardiac Output Measured by Impedance Cardiography During Incremental Exercise Testing of Young Normal (Group A), Older Normal (Group B) and Post Myocardial Infarction (Group C) Subjects.

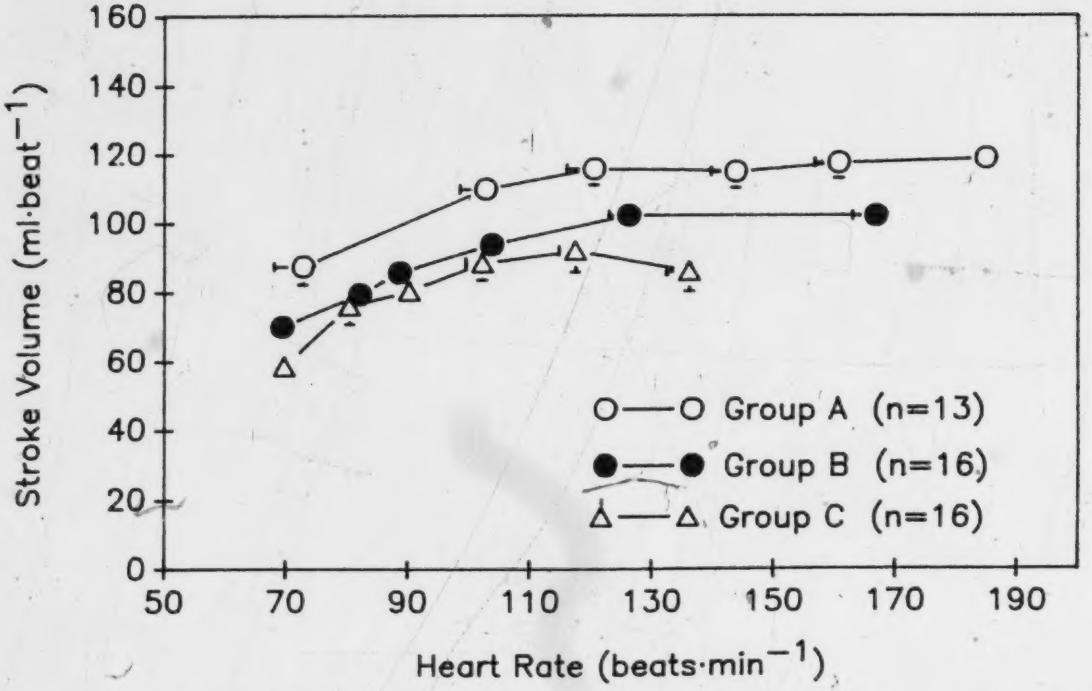

Figure 3.3 : Changes in Stroke Volume Measured by Impedance Cardiography During Incremental Exercise Testing of Young Normals (Group A), Older Normals (Group B) and Post Myocardial Infarction (Group C) Subjects.

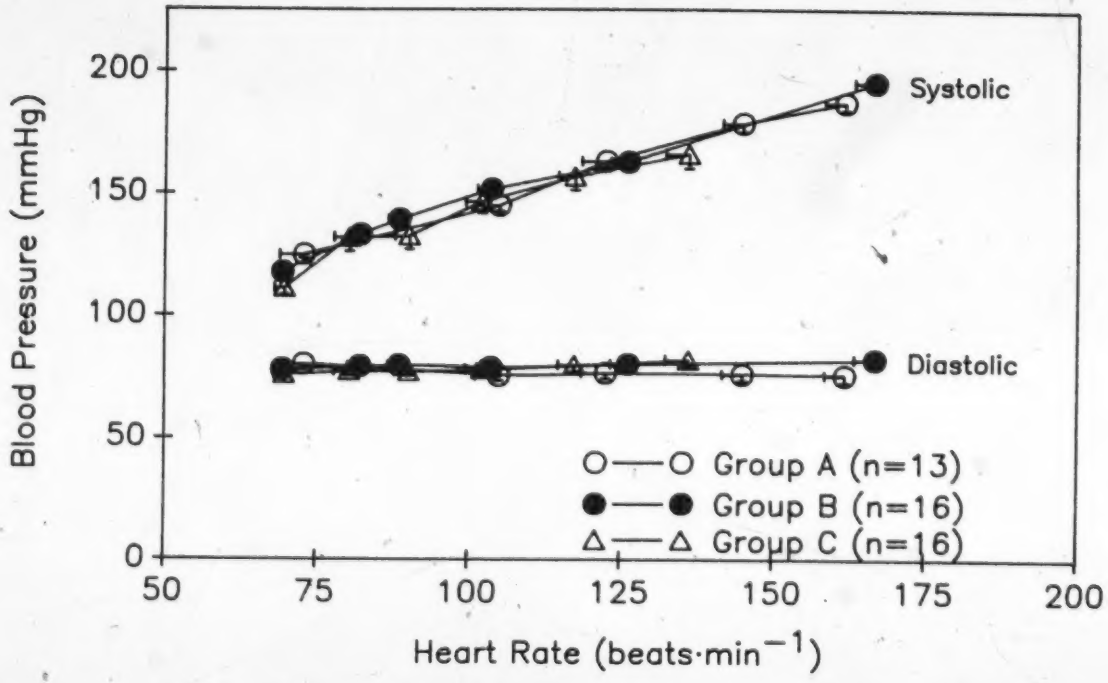

Figure 3.4 : Changes in Systolic and Diastolic Blood Pressure of Young Normals (Group A), Older Normals (Group B) and Post Myocardial Infarction (Group C) Subjects During Incremental Exercise Testing.

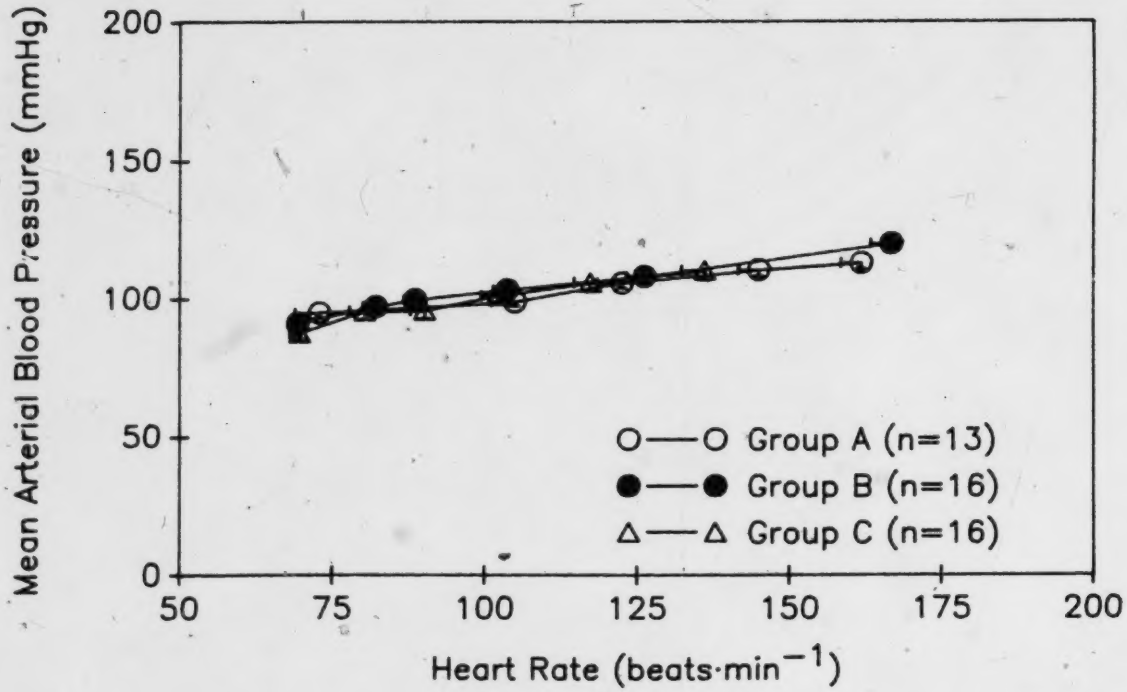

Figure 3.5 : Changes in Mean Arterial Blood Pressure of Young Normals (Group A), Older Normals (Group B) and Post Myocardial Infarction (Group C) Subjects During Incremental Exercise Testing.

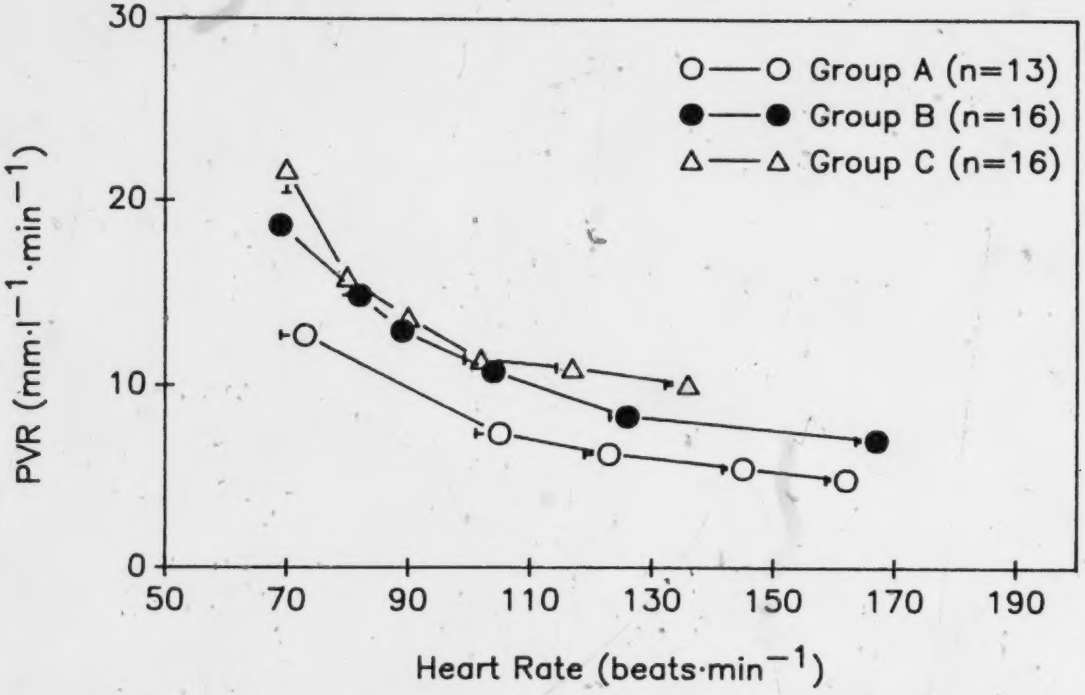

Figure 3.6 : Changes in Peripheral Vascular Resistance of Young Normals (Group A), Older Normals (Group B) and Post Myocardial Infarction (Group C) Subjects During Incremental Exercise Testing.

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CHAPTER 4

A RATE ADAPTING ATRIOVENTRICULAR DELAY IN ATRIAL TRACKING PACEMAKERS

INTRODUCTION

Dual chamber pacing has the advantage of allowing rate responsiveness along with the maintenance of AV synchrony. Thus, these pacemaker units are thought to closely mimic the natural cardiac response to physical stress such as exercise.

In the previous chapter it was shown that the timing of the PR interval varies during exercise in subjects without pacemakers and, in fact, conduction time decreases with a concomitant increase in heart rate. If this relationship is applied to dual chambered pacemakers, then it is desirable to assess any change in stroke volume and cardiac output that occurs in a sample of pacemaker patients utilizing a rate dependant AV delay. The normal stroke volume response to upright exercise is a gradual increase from resting values to a peak value at heart rates of 110 - 120 beats·min^{-1} (2). Cardiac output continues to increase beyond this point due to further increases in heart rate.

The purpose of this study was to observe the stroke volume response during submaximal exercise of subjects with atrial tracking pacemakers utilizing a rate adapting AV delay. For comparison, values obtained with a constant AV delay will be measured at matched heart rates. It is hypothesized that a rate

adapting AV delay will allow a pattern of stroke volume response in this group of subjects comparable to that found in normal subjects. In addition, values will be greater than those for the constant delay at matched heart rates.

METHODS

Subjects

Eight otherwise healthy subjects with complete AV block requiring cardiac pacing volunteered to participate in the study. AV block had been previously diagnosed by electrocardiogram, followed by surgical implantation of the pacemaker. In one subject, AV block was induced by surgical replacement of the mitral valve. The etiology was idiopathic in all other subjects. All were considered otherwise healthy by physical examination and history. Physical characteristics of the four women and four men are presented in Table 4.1.

Table 4.1

Physical Characteristics of Pacemaker Subjects

Subject Number	Gender	Age (years)	Height (cm)	Weight (kg)	Diagnosis
1	F	73	155.0	56.4	CHB
2	F	62	160.0	64.5	CHB
3	M	53	178.0	86.8	CHB
4	F	68	157.5	67.3	CHB
5	M	44	185.5	83.6	CHB, VR
6	F	53	159.0	64.1	CHB
7	M	71	183.0	83.6	CHB
8	M	67	175.0	72.0	CHB
Mean		61 $\pm$ 3.4			

CHB - Complete Heart Block VR - Valve Replacement

All subjects but one were implanted with a dual chamber pacemaker operating in the VDD or atrial tracking mode; a single subject was implanted with a single chamber pacemaker that was also atrial tracking (see Table 4.2). All were able to intrinsically increase their atrial rate but were dependant upon the pacemaker to provide a ventricular stimulus. None of the subjects were taking any cardiac medications at the time of the study.

Table 4.2

Pacemaker Type and Settings

Subject Number	Pacemaker Type	LRL (beats)	AV Delay (msec)	URL (beats)
1	Cordis Sequicor 233F *	50	150	151
2	Medtronic Symbios 7006 +	50	150	150
3	Medtronic Symbios 7006 +	50	150	175
4	Medtronic Versitrax II 7000A +	50	150	150
5	Cordis Sequior 233F *	50	150	151
6	Medtronic Symbios 7006 +	50	150	150
7	Medtronic Symbios 7006 +	50	150	150
8	Enertrax 7100 +	50	150	150

LRL - Lower Rate Limit
URL - Upper Rate Limit
* Cordis Corp., Miami.
+ Medtronic Inc.,Minneapolis.

All subjects were physically active therefore able to undertake the exercise protocols. Generally, subjects with pacemakers tend to be older, sedentary individuals. The ability to complete the exercise protocol was a consideration in recruting subjects. All subjects walked on a regular basis or participated in low level activities such as curling or cycling. One subject had been involved in aerobics classes on a

regular basis but had stopped several months prior to testing. No quantification of exercise capacity had been previously done.

Plan of the Study

Subjects performed 2 separate exercise tests on a bicycle ergometer following the safety guidelines of the American College of Sports Medicine (1). Test 1 established the individuals' heart rate response to a progressive loading protocol. No changes were made to the pacemaker during this test. The exercise endpoint was a heart rate of approximately 130 beats·min^{-1}. This was chosen as the highest heart rate to be assessed as 2:1 AV block could occur in the pacemaker as the preset upper rate limit was approached (4). The power outputs from Test 1 were used to obtain the necessary heart rates in Test 2. Heart rate was seen as the key factor; various power outputs were utilized to produce the required heart rates. Thus, actual power outputs used for Test 2 varied between individuals.

The purpose of Test 2 was to assess stroke volume and cardiac output produced with a rate adapting AV delay. For comparison, these parameters were also measured at similar heart rates at a constant AV delay of 200 msec. The relationship of PR interval, or AV delay as it is known in pacemakers, to heart rate was established in normal subjects and post myocardial infarction patients in another part of this study and predicted by means of a regression equation for the pooled data (see

Chapter 3). The precise relationship could not be matched in the pacemaker units. Only 25 msec. increments are available for programming the AV delay, limiting the available settings. In order to obtain several measurement points, the AV delays of 175,150 and 125 were chosen as being closest to the predicted intervals. The slope of the rate adapting AV delay varied from that of the regression equation established (Figure 4.1). Thus, the heart rate to AV delay relationship was as follows:

Heart Rate (beats·min^{-1})	Rate Adapting AV Delay (msec)	Predicted from Regression (msec)
70	200	163
80	175	159
90	150	154
105	150	148
130	125	136

This relationship known as the rate adapting AV delay was used during Test 2. The constant of 200 msec. was chosen as it represented the normal resting delay, is often used in pacemaker programming and would allow determination of the greatest difference.

Exercise Protocols

Subjects reported to the Central and Northern Cardiac Rehabilitation Centre for exercise testing, they were asked to refrain from the use of caffeine for two hours prior to testing. Procedures were explained and written informed consent obtained. Prior to Test 1, electrodes for 12 lead ECG monitoring as well

as impedance cardiography were attached along with a phonocardiogram. With the subject seated in the upright position on an electrically braked bicycle ergometer (Seimens Model EM840), resting measurements were obtained. The subject then pedalled at 50 rpm starting at a power output of 20 watts. Every 3 minutes the power output was increased by 20 watts until the subject reached the heart rate endpoint. Blood pressure was measured using a mercury sphygmomanometer during the second minute of each stage; stroke volume was measured at the end of each stage via impedance cardiography. Heart rate was continuously monitored through the Marquette Case computer assisted ECG system for exercise (Marquette Electronics, Milwaukee).

Upon completion of Test 1, the subject was removed from the testing area and allowed to rest for 30 minutes before commencing Test 2. When the subject returned to the testing laboratory they again assumed an upright position seated on the ergometer and resting values were measured to assure a resting heart rate within 10% of that of Test 1. The AV delay of the pacemaker was reprogrammed to 200 msec. and stroke volume measured. The subject pedalled at 50 rpm for a total of 5 minutes at each power output stage. During each stage the subject would cycle for 3 minutes to achieve steady state, whereupon stroke volume would be measured and the AV delay reprogrammed. The subject would then continue for another 2 minutes with the same power output at the end of which stroke

volume was again measured (see Figure 4.2 for design).

The order of constant or adapting AV delay was randomly assigned to each individual using a table of random numbers. Thus, the constant AV delay would be programmed during the first 3 minutes of each stage with the adapting AV delay programmed during the second 2 minute portion of that stage or the adapting AV delay would be first with the constant AV delay second. Blood pressure was measured during the second and fourth minutes of each stage. A Borg Scale reading of perceived exertion was taken at the two and one-half and four and one-half minute mark of each stage.

Statistical Analysis

Data for Test 2 was grouped relative to the heart rate levels of 70, 80, 90, 105 and 130 beats·min^{-1} referred to as Levels I, II, III, IV and V respectively. Values are reported as mean $\pm$ standard error of the mean (SEM). Paired t-tests were performed on the variables heart rate, stroke volume, cardiac output and blood pressure to assess any significant differences at $p < 0.05$. An analysis of covariance was used to estimate the difference between the heart rate-stroke volume relationship for the rate adapting AV delay versus the constant AV delay. The $p<0.05$ level was taken as significant.

RESULTS

The first exercise test was performed to establish the individual's heart rate response to a progressive load. Results of heart rate relative to power output are reported in Table 3. Subject # 6 had an extremely high resting heart rate prior to Test 1, this was attributed to apprehension as it was subsequently lower prior to Test 2.

Table 4.3

Heart Rate Response (beats·min^{-1}) of Pacemaker Subjects to Exercise - Test 1

Subject Number	Rest	Power Output (watts) 20	40	60	80	100	Peak Exercise
1	72	80	84	102	120		120
2	74	97	110	132			132
3	60	73	78	88	110	130	130
4	88	118	130				130
5	68	84	102	120	140		140
6	102	118	138				138
7	84	97	104	106	114		114
8	65	74	84		110	130	130
Mean	76.6	92.6	103.8	109.6	118.8	130.0	129.3
SEM	4.6	6.0	7.2	6.8	5.0	0.0	2.9

Throughout Test 1 the AV delay was 150 msec. While sitting on the bicycle ergometer, subjects had a mean resting heart rate of 76.6 ± 4.6 beats·min^{-1} and a stroke volume of 63.6 ± 7.5 ml·beat^{-1}. At peak exercise mean heart rate increased to 129.3 ± 2.9 beats·min^{-1} with a mean stroke volume of 62.8 ± 11.1 ml·beat^{-1} (see Table 4.5). Cardiac output thus

increased from 4.9 ± 0.7 $l \cdot min^{-1}$ at rest to 8.1 ± 1.4 $l \cdot min^{-1}$ at peak exercise (see Table 4.6). Power output at peak exercise ranged from 40 to 100 watts.

Systolic blood pressure rose gradually in all subjects. Resting levels of 128 ± 5 mmHg increased to a peak level of 176 ± 10 mmHg. Meanwhile diastolic pressure showed a slight rise in most subjects from a resting level of 80 ± 4 mmHg to 87 ± 4 mmHg at peak exercise. Thus, mean arterial pressure for the group rose slightly from 96 ± 4 mmHg at rest to 116 ± 5 mmHg at peak exercise.

Systolic pressure only increased from 108 to a maximum of 120 mmHg in Subject # 5. This individual also showed a decline in stroke volume and a slight rise in diastolic blood pressure with exercise.

Table 4.4

Stroke Volume Response ($ml \cdot beat^{-1}$)
of Pacemaker Subjects to Exercise - Test 1

Subject Number	Power Output (watts)						
	Rest	20	40	60	80	100	Peak Exercise
1	38.4	50.2	53.8	45.9			45.9
2	40.7	47.8	37.5	31.3			31.3
3	65.5	75.9	82.8	79.7	61.4	50.1	50.1
4	40.9	40.6	36.8				36.8
5	67.1	56.8	49.4	40.9	46.3		46.3
6	68.4	78.8	114.0				114.0
7	97.6	98.6	100.8	131.3	115.7		115.7
8	90.3	83.8	65.0		65.8	62.6	62.6
Mean	63.6	66.6	67.5	66.5	67.0	56.4	62.8
SEM	7.5	6.8	9.6	16.2	11.5	4.4	11.1

Table 4.5

Cardiac Output Response ($l \cdot min^{-1}$)
of Pacemaker Subjects to Exercise - Test 1

Subject Number	Power Output (watts) Rest	20	40	60	80	100	Peak Exercise
1	2.8	4.0	4.5	5.0	5.5		5.5
2	3.0	4.6	4.1	4.1			4.1
3	3.9	5.5	6.5	7.0	6.6	6.5	6.5
4	3.6	4.8	4.8				4.8
5	4.6	4.8	5.0	4.9	6.5		6.5
6	7.0	9.3	15.7				15.7
7	8.2	9.6	10.5	13.9	13.2		13.2
8	5.9	6.2	5.5		7.2	8.1	8.1
Mean	4.9	6.1	7.1	7.0	7.8	7.3	8.1
SEM	0.7	0.7	1.3	1.6	1.2	0.6	1.4

Table 4.6

Systolic Blood Pressure Response (mmHg)
of Pacemaker Subjects to Exercise - Test 1

Subject Number	Power Output (watts) Rest	20	40	60	80	100	Peak Exercise
1	120	136	146	166	166		166
2	134	190	192	200			200
3	144	168	170	174	200	220	220
4	144	186	186				186
5	108	124	124	120	120		120
6	110	136	170				170
7	140	160	160	160	178		178
8	120	130	140		170	170	170
Mean	128	154	161	164	167	195	176
SEM	5	9	8	12	12	18	10

Table 4.7

Diastolic Blood Pressure Response (mmHg)
of Pacemaker Subjects to Exercise - Test 1

Subject Number	Rest	Power Output (watts) 20	40	60	80	100	Peak Exercise
1	70	70	68	70	70		70
2	90	98	96	94			94
3	96	98	98	94	96	104	104
4	80	90	90				90
5	74	76	80	84	84		84
6	80	90	90				90
7	90	100	90	90	90		90
8	56	60	60		70	70	70
Mean	80	85	84	86	82	87	87
SEM	4	5	5	4	5	12	4

Table 4.8

Mean Arterial Blood Pressure Response (mmHg)
of Pacemaker Subjects to Exercise - Test 1

Subject Number	Rest	Power Output (watts) 20	40	60	80	100	Peak Exercise
1	87	92	94	102	102		102
2	105	129	128	129			129
3	112	121	122	121	131	143	143
4	101	122	122				122
5	85	92	95	96	96		96
6	90	105	117				117
7	107	120	113	113	119		119
8	77	83	87		103	103	103
Mean	96	108	110	112	110	123	116
SEM	5	6	5	5	6	14	5

In four of the eight subjects stroke volume failed to increase much above resting values or declined as heart rate increased. This group showed an overall decrease in stroke volume from 59.7 ± 10.3 ml·beat^{-1} at rest to a mean value of 44.2 ± 5.9 ml·beat^{-1} at peak exercise (Figure 4.3). Corresponding cardiac output for this subgroup was 4.3 ± 0.5 l·min^{-1} at rest and 5.9 ± 0.8 l·min^{-1} at peak exercise.

Three subjects were unable to maintain an increase in stroke volume when heart rate increased above 100 beats·min^{-1}. Grouped values for stroke volume were 67.2 ± 14.0 ml·beat^{-1} at rest, 86.8 ± 19.5 ml·beat^{-1} at 60 watts and 70.6 ± 18.5 ml·beat^{-1} at peak exercise (Figure 4.4). Cardiac output for this subgroup was 5.0 ± 1.4 l·min^{-1} at rest, 8.7 ± 2.2 l·min^{-1} at 60 watts and 8.4 ± 2.0 l·min^{-1} at peak exercise. Subject # 6 had a continued increase in stroke volume with progressive heart rate increase but was only able to complete 2 levels of exercise (Figure 4.4).

During Test 2 the rate adapting AV delay was programmed corresponding to the heart rate level. Not all subjects were represented at all Levels; some subjects had resting heart rates higher than Level I. Therefore, their resting values were classified in the level appropriate to the heart rate.

Mean values at Level I were heart rate 70.0 ± 2.3 beats·min^{-1}, stroke volume 60.1 ± 8.9 ml·beat^{-1} and cardiac output 4.1 ± 0.6 l·min^{-1} at an AV delay of 200 msec. At the subsequent levels, as heart rate increased, stroke

Table 4.9

Hemodynamic Values During Submaximal Exercise
for Constant and Adapting AV Delays During VDD Pacing
Test 2

Level	I (n = 5)	II (n = 6)	III (n = 8)	IV (n = 6)	V (n = 6)
Constant AV Delay 200 msec.					
Heart Rate ($beats \cdot min^{-1}$)	70.0 ± 2.3	80.8 ± 2.5	91.1 ± 1.8	106.5 ± 2.7	124.5 ± 1.1
Stroke Volume ($ml \cdot beat^{-1}$)	60.1 ± 8.9	58.8 ± 5.2	56.7 ± 3.8	55.9 ± 4.0	48.7 ± 2.7
Cardiac Output ($l \cdot min^{-1}$)	4.1 ± 0.6	4.7 ± 0.3	5.2 ± 0.3	6.0 ± 0.5	6.0 ± 0.3
Borg Scale		8 ± 0.5	11 ± 0.5	12 ± 0.9	15 ± 0.6
Rate Adapting AV Delay					
Heart Rate ($beats \cdot min^{-1}$)		81.8 ± 2.4	87.5 ± 1.3	105.2 ± 2.6	122.0 ± 1.8
Stroke Volume ($ml \cdot beat^{-1}$)		60.2 ± 6.1	61.8 ± 4.0	54.2 ± 3.6	55.8 ± 5.3
Cardiac Output ($l \cdot min^{-1}$)		4.8 ± 0.4	5.4 ± 0.4	5.7 ± 0.4	6.8 ± 0.6
Borg Scale		8 ± 0.7	11 ± 0.8	12 ± 1.1	15 ± 0.7
AV Delay (msec)	200	175	150	150	125

n = number of subjects who completed the level.
Values are Mean ± SEM.

Table 4.10

Blood Pressure Values During Exercise
for Constant and Adapting AV Delays During VDD Pacing
Test 2

Level	I (n = 5)	II (n = 6)	III (n = 8)	IV (n = 6)	V (n = 6)
Constant AV Delay 200 msec.					
Systolic BP (mmHg)	129 ± 14	125 ± 10	132 ± 7	157 ± 10	159 ± 10
Diastolic BP (mmHg)	74 ± 8	74 ± 5	80 ± 4	81 ± 4	78 ± 3
Mean Arterial BP (mmHg)	92 ± 9	91 ± 8	97 ± 4	107 * ± 6	105 ± 3
Rate Adapting AV Delay					
Systolic BP (mmHg)		125 ± 9	135 ± 8	161 ± 12	163 ± 9
Diastolic BP (mmHg)		77 ± 6	78 ± 4	84 ± 4	79 ± 2
Mean Arterial BP (mmHg)		93 ± 6	97 ± 4	110 * ± 6	107 ± 4
AV Delay (msec)	200	175	150	150	125

n = number of subjects who completed the level.
Values are Mean ± SEM.
* Significant Difference, $p<0.05$.

volume gradually declined with both the constant and rate adapting AV delays (Figure 4.5). Cardiac output increased in both cases (Figure 4.6). Mean values at Level V were heart rate 124.5 ± 1.1 beats·min^{-1}, stroke volume 48.7 ± 2.7 ml·beat^{-1} and cardiac output 6.0 ± 0.3 l·min^{-1} at an AV delay of 200 msec. At an AV delay of 125 msec heart rate was

122 ± 1.8 beats·min^{-1}, stroke volume 55.8 ± 5.3 ml per beat and cardiac output 6.8 ±0.8 l·min^{-1}. This represents a difference of 13 % in stroke volume and 12% in cardiac output, the greatest difference at any level.

There were no significant differences in rate adapting versus constant AV delay at any of the levels for heart rate, stroke volume, cardiac output, systolic and diastolic blood pressure. There was a significant difference ($p<0.05$) in mean arterial blood pressure at Level IV.

Analysis of covariance (Table 12) showed no significant difference between the constant AV delay and the rate adapting AV delay for the slope or elevation of the stroke volumes (Figure 4.7).

Table 4.11

Analysis of Covariance for Stroke Volume-Heart Rate Relationship with Rate Adapting AV Delay versus Constant AV Delay During VDD Pacing

	F	df	Decision p<0.05
Slope	0.003	1,48	Not Significant
Elevation	0.682	1,49	Not Significant

DISCUSSION

This study was undertaken to examine any changes in stroke volume during exercise in subjects with atrial tracking pacemakers when a rate adapting AV delay was utilized. A

constant delay of 200 msec. was used as the baseline for comparison. This constant represented the PR interval at rest established in normal and post myocardial infarction subjects in Chapter 3 of this study. As well, 150-200 msec. have been identified as the AV delays providing the optimal cardiac output at rest in pacemaker subjects (6,10). It was assumed that the greatest difference would be clearly visible when the rate adapting AV delay was compared to this constant.

The pacemaker subjects were considered otherwise healthy by history and physical examination. They were physically active on a regular basis in low intensity activities. The results of the initial exercise test suggest that this group have an abnormal stroke volume response to exercise. Hetherington et al (7) noted 2 patterns of abnormal stroke volume response in post myocardial infarction patients. The pacemaker subjects in this study showed similar patterns. Four subjects had no change or a decline in stroke volume with progressive exercise loads. Three initially increased their stroke volume but showed a 19% decline at peak exercise. One subject had a gradual increase in stroke volume but was only able to complete 2 exercise stages. Mean heart rate at any power output was greater in this group of subjects than any of the patient groups studied by Hetherington et al (7). Meanwhile, cardiac outputs were comparable suggesting the importance of heart rate response during exercise in the pacemaker group. It could be that afferent information from the exercising muscles acted to increase heart rate in an

attempt to maintain an increase in cardiac output to meet further exercise demands (12). Additionally, an increase in sympathetic drive could act to shunt blood from the non-exercising muscles resulting in increased arterial pressure. The pattern of mean arterial pressure rise in these pacemaker subjects did match that seen in the post myocardial infarction patients and was excessive when compared to the normal response.

The second test protocol required that stroke volumes be assessed at matched heart rates for the constant and adapting AV delays. While 130 beats·min^{-1} was the highest heart rate examined, some of the older subjects were approaching a greater percentage of their maximum exercise capacity than their younger counterparts. This heart rate represents 87% of predicted maximum for a 70 year old but only 72% of maximum for a 40 year old. It could be that they were pushed further toward the failing upper end of their stroke volume curve.

Due to the ease of use and the non-invasive nature of impedance cardiography subjects were able to complete several consecutive stages of exercise. Other studies have assessed the effect of different AV delays only at rest (2,10,14) or at only one level of exercise (11). The protocol in this study required several changes in AV delay with a short adaptation time before impedance measurements. If a rate adapting AV delay were programmed into a pacemaker it would have to change as rapidly as the accompanying heart rate increase. Thus, it was deemed practical to examine the rate adapting AV delay in this manner.

Random ordering of constant and rate adapting delay was utilized to minimize the influence of one setting upon the other.

Certain methodological considerations did exist with the use of impedance cardiography. The impedance waveforms did not show the clear deflection point denoting the onset of ejection as normally seen. Consequently, carotid pulse tracings were recorded simultaneously with impedance cardiography in 5 pacemaker subjects. Agreement for left ventricular ejection time was found at rest between the methods. Immediately following light exercise impedance cardiography was found to underestimate ejection time by 0.02 sec. which could result in a 4 - 10% difference in stroke volume. Despite this, it was felt that impedance cardiography provided a simple, inexpensive method to obtain sequential measurements during a progressive exercise test.

Two key variables for physiological pacing are the ability to increase pacing rate and the maintenance of AV synchrony. The group chosen for the study were able to intrinsically increase their atrial rate, but could not conduct the impulse down to the ventricles. Their pacemakers tracked this atrial activity and provided the sequential ventricular activation.

The importance of rate responsiveness is supported by the improvement in cardiac output reported by Karlof (8). A 20% increase in cardiac output during exercise was observed for atrial tracking pacing when compared to fixed rate VVI pacing. When the ventricular rates were matched this lessened to only a

8% difference in cardiac output during exercise. Also, Pehrsson (13) reported an increase in physical work capacity of 20% with rate matched VVI pacing when compared to fixed rate VVI pacing. In both case the improvements were felt to be facilitated by the restoration of heart rate response.

The subjects in the present study were able to increase cardiac output progressively in response to increasing power outputs. This occurred despite an essentially unchanged stroke volume, indicating the significance of the ability to increase ventricular rate.

Still, Karlof (8) suggested that the higher cardiac outputs could not be attributed to rate response alone. While there was no significant difference when comparing rate matched VVI pacing with VAT pacing, cardiac output was 18% higher at rest and 8% higher during exercise with VAT. It was felt that this must be due to AV synchrony as it could not be attributed to heart rate differences.

If this contention is supported there would be a need to adapt the length of the AV delay relative to the pacing rate. In normal subjects the AV interval decreases as heart rate increases, apparently to maintain optimal timing between the atria and ventricles. There is increased ventricular filling with intervals of 50-200 msec. compared to intervals outside this range (16). The timing of atrial systole is also important in assisting with the closure of the AV valves. Regurgitation of blood into the atria could occur when the ventricules

contract, resulting in a decrease in effective stroke volume. It follows that it would be advantageous to maintain optimal timing with pacemaker subjects.

The finding of no significant difference in hemodynamic values between a rate adapting AV delay and the constant delay of 200 msec. in this study is contrary to the findings of Ritter et al (14). Measurements were made during catheterization with the AV delay shortened relative to an increasing heart rate. When compared to constant AV delays, the most favorable hemodynamics were found with the adapting delay. Still, this study was performed at rest in the supine postion therefore cannot be extented to the exercise situation.

Mehta et al (11) found the highest cardiac output during exercise was produced with an AV delay of 75-80 msec. While various AV intevals were assessed only one heart rate level was examined. The question of a rate adapting AV delay was not really addressed.

Several studies (5,8,9) support the contention that AV synchrony may have a positive influence on cardiac output at rest while during exercise this effect decreases. In normal subjects during exercise an increase in stroke volume results from a combination of the Frank-Starling mechanism responding to increased venous return, enhancement of the inotropic state and a reduction of peripheral vascular resistance. In order to invoke the Frank-Starling mechanism there is a need to increase preload. This occurs during exercise with enhanced venous

return from the constricted systemic vasculature. If the ventricle is stiff or already overfilled, this increased preload will produce high end diastolic pressures. Greenberg et al (5) reported that the atrial contribution is less effective in influencing stroke volumes when filling pressure is elevated. This was especially evident in patients with left ventricular dysfunction.

It may be that the subjects in this study had varying degrees of left ventricular dysfunction. This is suggested by the abnormal stroke volume curves from Test 1. Shortening the AV delay relative to increasing heart rates had no effect on stroke volumes as the atrial contribution failed to enhance effective filling.

The pacemakers assessed in this study had only 25 msec. increments available for changing the AV delay. At 12msec/10 beats the relative change in AV delay was far greater than that observed in various non-paced subject groups. When expressed as slopes, the rate adapting AV delay was -1.14 while the value for non-paced subjects was -0.45. In order to adapt to the pacing rate, further refinements in dual chambered pacemakers are required to provide finer increments for change in the AV delay.

Mehta et al (11) found the greatest stroke volume during exercise near a heart rate of 102 beats·min^{-1} was obtained with an AV delay of 75 msec. in pacemaker subjects with normal ventricular function. This was much shorter than the range predicted from any of the non-paced groups. Using

echocardiography, Von Bibra et al (17) found that at rest a short AV delay of 50 or 75 msec. maximized ventricular filling time. It appears that while there is an optimal physiological range of the AV interval for normal subjects any effect of this range upon pacemaker subjects is so subtle that it could be unnoticed. In this study, an AV delay of 125 msec. at a heart rate near 125 beats·min^{-1} produced a 13% increase in stroke volume when compared to the constant of 200 msec.

It has also been suggested that the mechanical delay associated with atrial sensing can act to actually lengthen the effective delay beyond the programmed value (11). For instance, instead of the programmed value of 150 msec, the actual delay could be 160 msec. It may be that the rate adapting relationship needs to be shortened to the range of 150-75 msec. to be effective.

It could be that subjects with normal left ventricular function would benefit from a rate adapting AV delay. It may also be that the value for the relative change in AV delay is outside the range found in non-paced subjects.

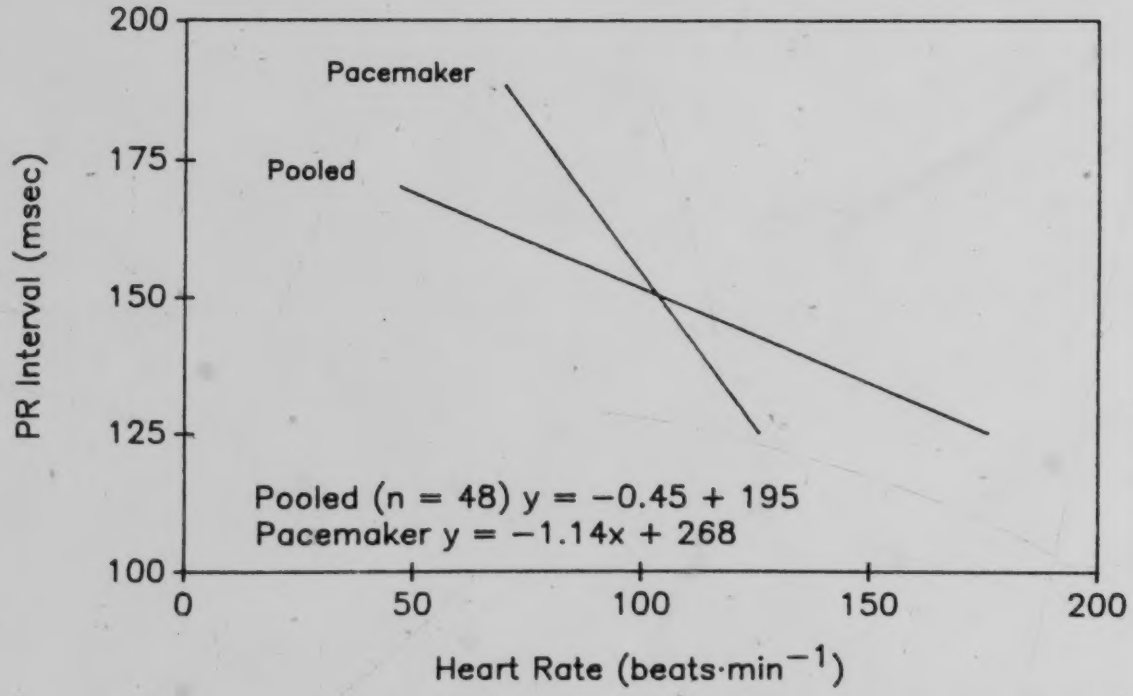

Figure 4.1 : **Linear Regression for Pooled Data from Normal and Post Myocardial Infarction Subjects and Rate Adapting AV Delay Dictated by Technical Limitations Actually Used in Pacemakers.**

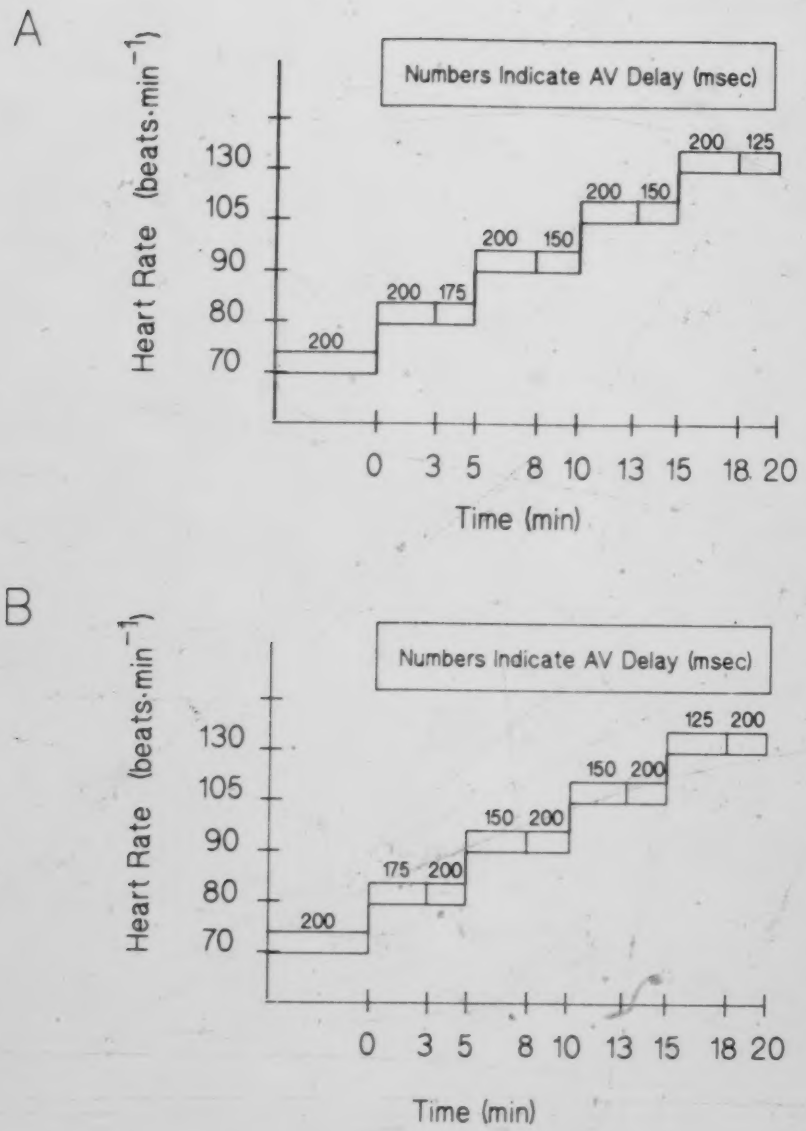

Figure 4.2: Design for Test 2. Subjects were randomly assigned A or B.

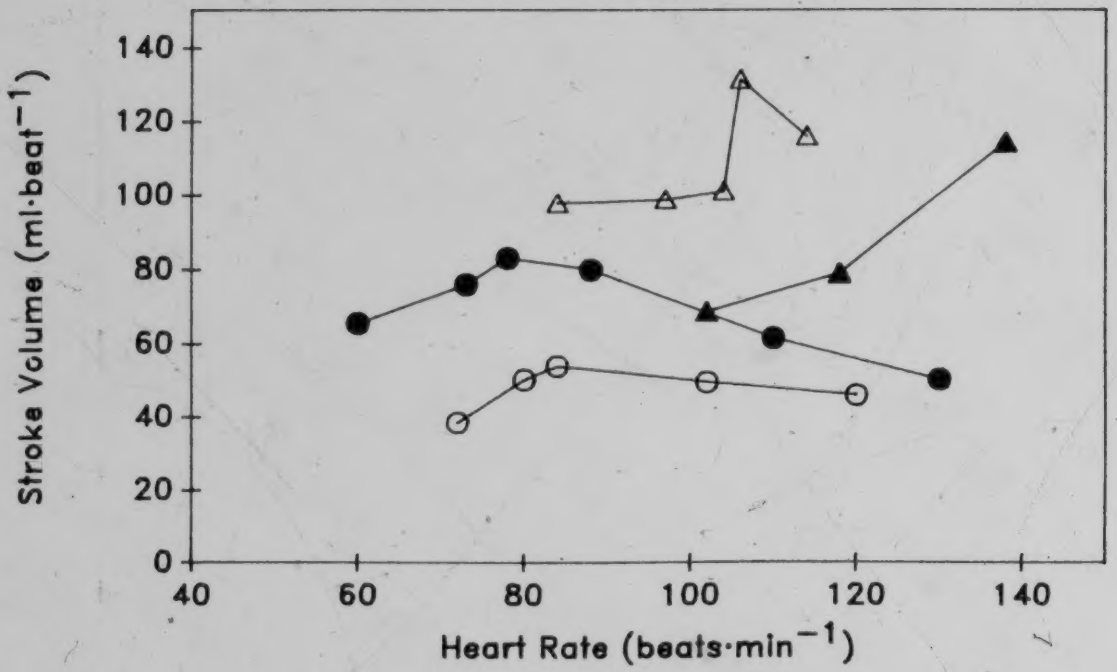

Figure 4.3 : **Changes in Stroke Volume of Pacemaker Subjects During Incremental Exercise Testing (Test 1). Subjects with an Initial Increase in Stroke Volume.**

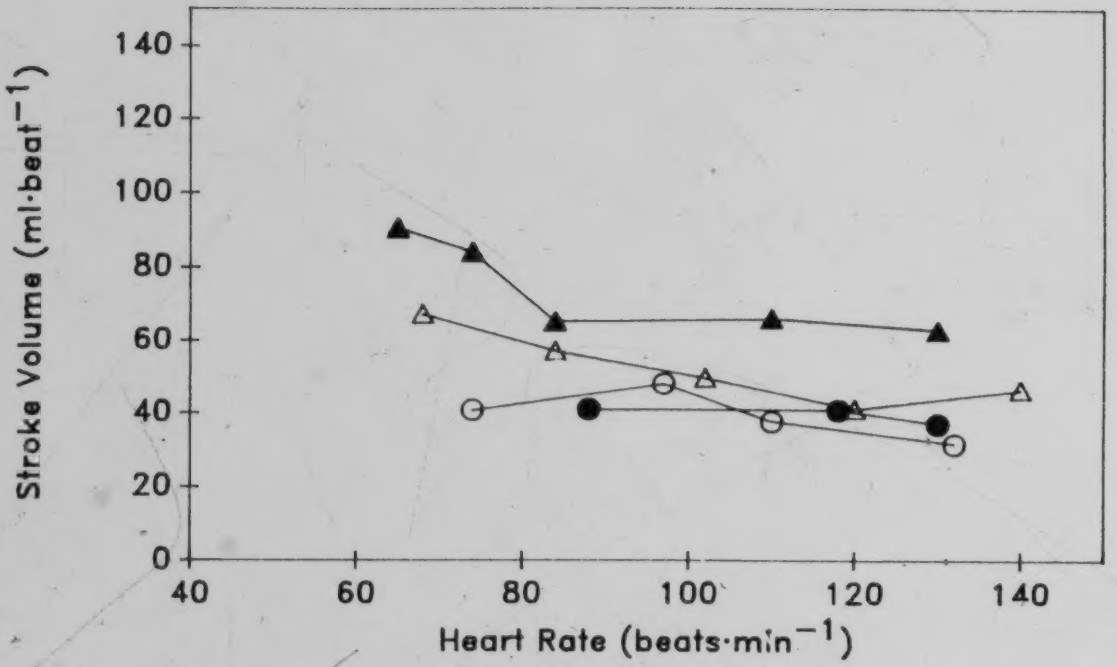

Figure 4.4 : Changes in Stroke Volume of Pacemaker Subjects During Incremental Exercise Testing (Test 1). Subjects with a Flat or Declining Stroke Volume Response.

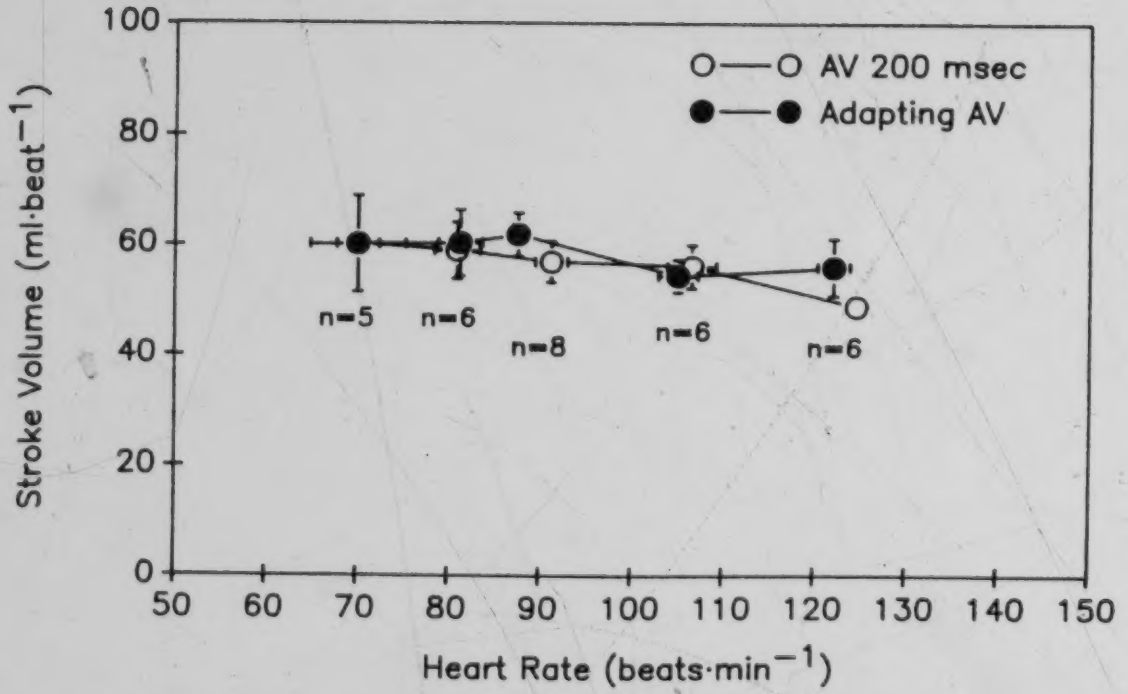

Figure 4.5 : Changes in Stroke Volume of Pacemaker Subjects During Rest and Submaximal Exercise. VDD Pacing with Constant (200 msec) and Rate Adapting AV Delays.

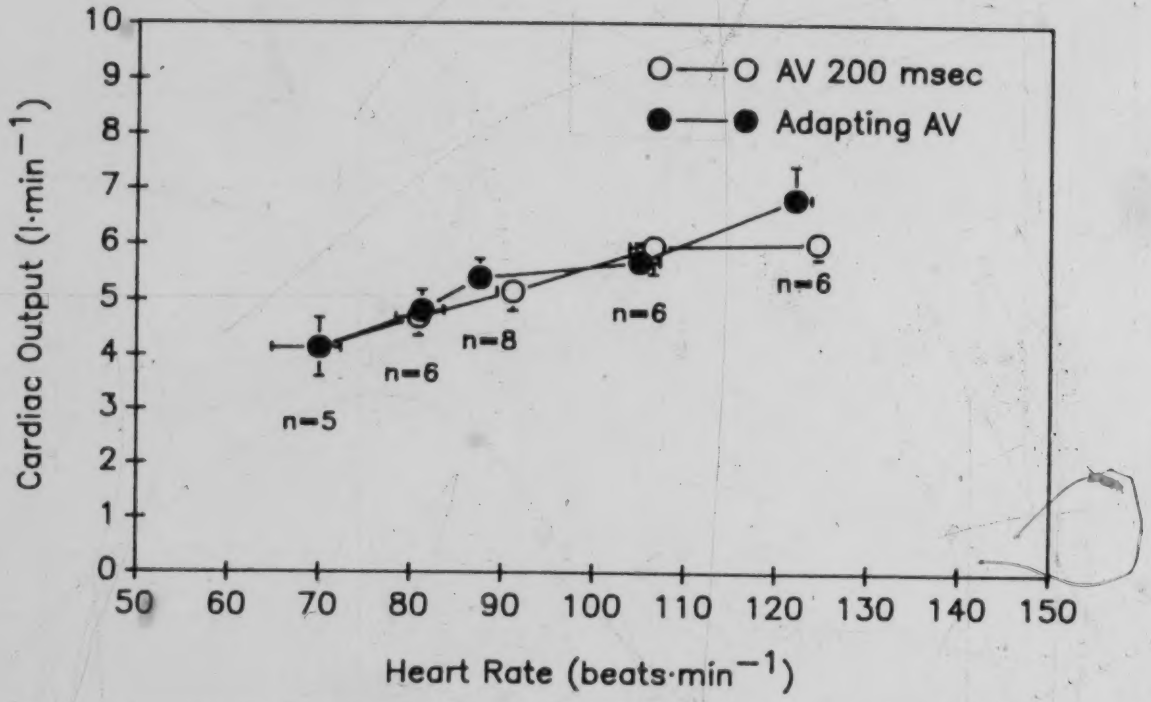

Figure 4.6 : Changes in Cardiac Output of Pacemaker Subjects During Rest and Submaximal Exercise. VDD Pacing with Constant (200 msec) and Rate Adapting AV Delays.

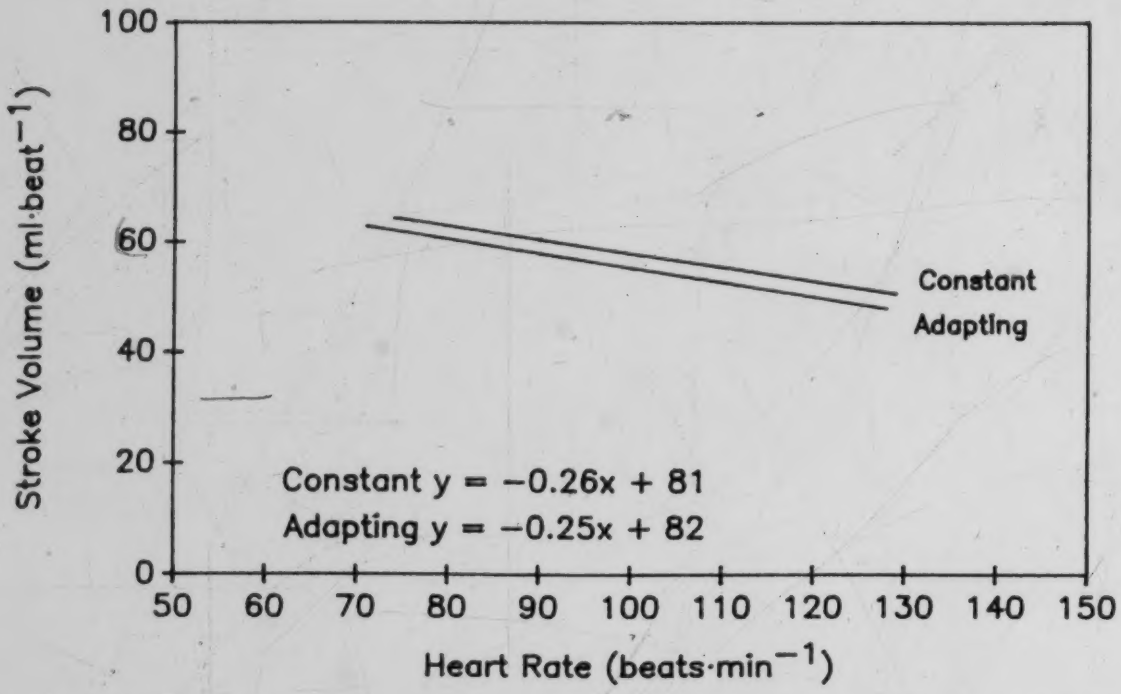

Figure 4.7 : **Linear Regression of Stroke Volume for Constant (200 msec) and Adapting AV Delays with VDD Pacing During Rest and Submaximal Exercise.**

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CHAPTER 5

GENERAL DISCUSSION AND CONCLUSIONS

Dual chambered pacing is a recommended treatment for subjects with symptomatic bradycardia resulting from complete atrioventricular (AV) block. The theoretical advantage of this type of pacing is the restoration of rate responsiveness along with AV synchrony, resulting in an increased cardiac output with exercise. In order to provide optimal exercise performance it was thought necessary to adjust the timing of the atrial contraction relative to the ventricular contraction following some algorhythm. In non-paced subjects this timing is adjusted through natural mechanisms which shorten the PR interval as the heart rate increases.

The results from this series of investigations indicate that there is a negative linear relationship between heart rate and PR interval in both normal subjects ($r=0.73$, younger subjects ; $r=0.77$, older subjects) as well as post myocardial infarction patients ($r=0.49$). During a progressive exercise test, both heart rate and PR interval could be obtained from a recorded electrocardiogram. Individual profiles could then be generated. While all groups showed the general trend of increased conduction with increased heart rate, the post infarction patients were more likely to demonstrate disruptions in this relationship. This could be a result of physical damage to the heart.

The heart rate - PR interval relationship could not be precisely matched in the pacemakers assessed due to technical limitations. The available increments for changing the AV delay did not provide a fine enough scale to match the slope of -0.45 predicted by the relationship in the three groups. However, a rate adapting AV delay (slope -1.14) matching the relationship as close as possible could be manually programmed for use during exercise testing.

Impedance cardiography provided an easy to use, inexpensive and non-invasive method of measuring stroke volume and cardiac output in a group of pacemaker subjects. Measurements during exercise may result in a slight underestimation of stroke volume due to an underestimation of ejection time. When compared to carotid pulse tracings, a 4-10% under estimation of stroke volume could consistently occur at exercise levels. Ejection times at rest were consistent in both methods.

During preliminary exercise testing it was found that most pacemaker subjects presented with an abnormal stroke volume response consistent with left ventricular dysfunction. When either the rate adapting AV delay or the constant AV delay was incorporated into the pacemaker the subject group showed a decrease in stroke volume with progressive exercise. This suggests that pacemaker subjects with signs of left ventricular dysfunction do not benefit from a rate adapting AV delay. Still, due to limitations within the pacemaker units assessed, the predicted relationship could not be precisely matched. It

has been suggested that there is a lengthening of the effective AV delay beyond the programmed time due to the sensing of the intrinsic atrial contraction. Thus, it may be necessary to program a shorter AV delay than that observed in normal individuals for any particular heart rate. It has also been suggested that a non-linear relationship is required to provide optimal AV synchrony in pacemakers subjects with increased heart rates. To produce larger stroke volumes at higher heart rates it may be necessary to shorten the AV delay to a value 25-50 msec. less than utilized in the present study.

A small subject group resulted from the need to recruit individual's with similar types of pacemakers who could physically complete the necessary protocols. This small subject number along with the large variation seen in some of the measurements had a definate influence on the power of the study design.

At present, pacemaker subjects do not perform formalized routine exercise testing as part of their post-implantation care. Practical limitations to such exercise testing are the age of the the individual and the predicted activity level following implantation. Very elderly and inactive individuals may not be suitable for exercise testing, nor benefit from guidelines established from such testing.

In younger pacemaker subjects and those who indulge in regular physical activity, a routine exercise test could be scheduled 3-4 months following implantation to allow for

stabalization of lead connections. The purpose would be to establish exercise tolerance. One of the established progressive exercise protocols on the treadmill or bicycle could be used along with monitoring of the electrocardiogram. Information regarding heart rate or pacing rate response, fatigueability and abnormalities in electrocardiogram could be used to provide guidelines for activity. In addition, the upper rate limit could be determined based upon exercise testing. In the present study 2:1 AV block occurred in the pacemakers of 2 individuals prior to the onset of fatigue during exercise testing. The upper rate limit was reprogrammed at a higher setting with satisfactory results in enhancing daily activities.

Ideally, some quantification of left ventricular function would be obtained during exercise testing. Such non-invasive techniques as impedance cardiography or echocardiography could be utilized to provide profiles of stroke volume response. This information could form the basis of follow-up studies on cardiac performance with different types of pacemakers, response to exercise training and prognosis for ventricular function in pacemaker subjects.

Thus, the exercise performance of pacemaker subjects requires further study. Specific issues that need to be assessed are:

1. A comparison of stroke volume changes in pacemaker subjects as measured by impedance cardiography with other clinically accepted methods.

2. An assessment of the stroke volume response of pacemaker subjects during progressive exercise to profile and determine prognostic value.

3. An examination of the stroke volume response during progressive exercise testing utilizing a dual chambered pacemaker with finer increments for the change in AV delay to closely match the slope of the normal relationship.

4. An evaluation of the stroke volume response during progressive exercise testing using shorter AV delays for the rate adapting relationship. This could compensate for the possible lengthening of the delay due to atrial sensing.

5. An evaluation of the stroke volume response during progressive exercise testing utilizing a non-linear relationship for the rate adapting AV delay.

APPENDIX

REVIEW OF LITERATURE

Normal Atrioventricular Conduction

The normal spontaneous heart beat originates from the sino-atrial node, located on the posterior aspect of the heart near where the superior vena cava joins the right atrium. From this natural pacemaker, the electrical impulse is conducted via the atrial preferential pathways in the muscle (35) to the atrioventricular (AV) node. At the same time the impulse is conducted via Bachmann's bundle directly to the left atrium.

Located on the medial wall of the right atrium, the AV node is responsible for the principle delay in impulse conduction to the ventricles. Physiologically, this allows the atria to complete their contraction and the AV valves to close prior to the onset of ventricular systole (5).

The electrical phenomenon of AV conduction can be analysed from the surface electrocardiogram (12), with the P wave representing the spread of atrial depolarization, the QRS complex the spread of the ventricular excitation and the T wave representing ventricular repolarization. The PR interval is a measure of the time from the onset of atrial activation to the onset of ventricular activation. It can be broken down further to P wave duration of approximately 100 milliseconds (msec.), delay at the AV node of 40-80 msec. and approximately 20 msec.

for the impulse to pass through the Bundle of His, bundle branches and Purkinje fibres to the ventricular muscle. Thus the total time of the PR interval is 160-200 msec. near resting levels (12).

Atrioventricular Conduction Block

Abnormalities of conduction of the electrical impulse within the heart or AV blocks can occur at any level of the conduction system (35). It can be manifest as prolonged conduction known as first degree block or intermittent conduction called second degree block which is subsequently divided into Type I and Type II. In addition, there can be third degree or complete heart block where no conduction occurs.

Complete heart block can be congenital or aquired in nature and have varied etiologies. The most common locations of blocks are the bifurcating Bundle of His and the bundle branches (10) as well as the AV node (17). The loss of conduction fibres can result from structural events such as acute infarction and calcification or be associated with disease processes such as myocarditis, endocarditis, coronary insufficiency and idiopathic fibrosis (35,10).

As the electrical impulse is blocked from being conducted to the ventricles, the ventricular rate can drop to less than 40 beats per minute. This can produce symptoms from the low cardiac output; Stokes-Adams syncope, dizziness, weakness, congestive heart failure (35).

Permanent cardiac pacing is recommended therapy for symptomatic patients as well as those with diagnosed infranodal or intranodal block with extremely low heart rates (35,11,22).

Normal Heart Rate to PR Interval Relationship During Exercise

Astrand (2) notes that with dynamic exercise the increase in heart rate is linear with the increase in work. In addition, Lister et al (24) observed a shortening of the PR interval with spontaneous heart rate increases. This was attributed to the fact that the neuro-humoral stimuli which accelerate heart rate also enhance AV conduction.

Heart rate increases with exercise are initially due to the withdrawl of vagal tone followed by a continued increase in activity of the sympathetic nerves. Also, plasma concentrations of catecholamines increase with the intensity and duration of dynamic exercise (8).

Conduction can be influenced by the neural effects upon the AV junction, in particular the AV node (39,17). Sympathetic nerve stimulation results in a shortened AV conduction time, while vagal stimulation prolongs conduction time (5,24,39). Thus, it follows that with exercise there will be an increased heart rate and a decreased PR interval due to the neural and humoral influences.

Neural effects can produce some seemingly abnormal results. Several studies (3,14,23) have indicated that increased vagal tone in highly trained subjects is responsible for the

bradycardia and prolonged PR intervals at rest. In comparison to the general population the PR interval can be prolonged (greater than 200 msec.) and there is a high frequency of first and second degree AV block (24,14). Generally, exercise acts to normalize the PR interval in athletes as vagal influence is withdrawn and sympathetic factors begin to take affect.

Lister et al (24) studied the relationship between heart rate and atrioventricular conduction at rest and under the influence of exercise, isoproterenol and atropine. Fourteen subjects from 21 to 70 years of age were observed; ten were normal subjects with no known heart disease, while four were diagnosed as having coronary artery disease. Right heart catheterization was performed and an external pacemaker electrode placed in the right atrium. Atrial pacing was used in all cases to artificially increase the heart rate. Electrocardiograms were recorded at a paper speed of 100 millimeters per second ($mm \cdot sec^{-1}$) and the PR interval measured from these recordings.

With the subject at rest, atrial pacing rate was increased up to 160 beats per minute ($beats \cdot min^{-1}$) producing a prolongation of atrioventricular conduction time. Meanwhile, when the subject was performing supine steady state leg exercise it was found that the PR interval was shorter at any given paced heart rate.

Presumably, the accompanying sympathetic stimulus with exercise acted to decrease conduction time. When the heart was paced and

the subject essentially at rest, the prolonged conduction time reflected the lack of sympathetic influence. The response of the patient group was similar to that of the normal subjects.

Both the sympathomimetic drug isoproterenol and the parasympathetic blocker atropine acted to shorten the PR interval at any given paced heart rate, reflecting increased atrioventricular conductivity. Also, as the rate was increased, the PR interval was observed to decrease while still under the influence of these circulating drugs.

Simmoons and Hugenholtz (36) provided a quantitative description of the electrocardiogram from rest to maximal exercise in 56 healthy males aged 23-62 years. Exercise was performed on a bicycle ergometer with the power output increased by either 10 watts per minute or 30 watts every three minutes until subject exhaustion. Using the standard recording speed of 25 $mm \cdot sec^{-1}$ they found that the P waves encroached upon the preceding T waves at higher heart rates. Thus, they utilized the peak of the P wave to the beginning of the QRS complex for the measurement rather than the standard PR interval. It was found that from an average resting heart rate of 70 $beats \cdot min^{-1}$ the peak P-Q interval of 108 $\pm$ 16 msec. shortened to 72 $\pm$ 10 msec. at maximal exercise with a mean heart rate of 170 $beats \cdot min^{-1}$. This represents a decrease of 3.6 msec/10 beats in the interval from rest to maximal exercise.

Invasive methods were used by Daubert et al (9) to assess the relationship between PR interval and heart rate. Ten

healthy subjects ranging in age from 17 to 65 years, mean 47.6 ± 19.9 years. Catheter electrodes were inserted in the right atrium and tip of the right ventricle and connected to a dual chamber pacemaker set for sensing only. Intervals were measured by computer to within a 1 msec. accuracy using an averaged value over ten heart beats when rate was increasing. Resting values were recorded after ten minutes. The subject then completed a bicycle ergometer test starting at an initial power output of 20 watts with an increase of 10 watts per minute until exhaustion.

At rest the heart rate was 84.5 ± 9.2 beats·min^{-1} (mean ± standard deviation) and PR interval 169 ± 20.5 msec. Maximal exercise values were 163.3 ± 23.1 beats·min^{-1} and 141.4 ± 20.5 msec., respectively. This represented an average deviation of 4.0 ± 2.1 msec/10 beats. Correlations were determined for each individual with r values between 0.73 and 0.97, indicating a high linear relationship. No statistically significant correlation was observed between age and the PR interval variation.

In summary, there is a strong relationship between heart rate and PR as predicted by the common neuro-humoral influences. The correlations reported by Daubert support this idea. Additionally, the reported relative change in PR over 10 beats from rest to maximal exercise was found to be similar (9,36) over a wide range of ages.

Cardiac Output Response to Exercise

In order to meet the increased metabolic demands associated with exercise cardiac output increases in a linear fashion from rest to maximal. This can represent a change from 4 - 6 $l \cdot min^{-1}$ at rest up to 30 $l \cdot min^{-1}$ at maximal exercise in the well trained athlete (1). The integrated response of both heart rate and stroke volume accomplishes this change. Heart rate can increase three fold while stroke volume can double.

It has been well established that stroke volume increases from resting levels to reach maximum values at heart rates of 110 - 120 beats $\cdot min^{-1}$ in the normal subject during upright exercise. While stroke volume is maintained at this level, heart rate continues to increase with further exercise demands. Increases from resting levels of 70 to 200 beats $\cdot min^{-1}$ with exercise can be seen in the young adult (1).

Initial changes in heart rate are due to the withdrawl of vagal tone. In addition, increased sympathetic stimulation and elevated circulating catecholamines produces rate acceleration as well as peripheral changes that increase venous return to the heart (5). This increase in preload acts to invoke the Frank-Starling mechanism which produces an increased stroke volume (5,7). In addition, an increase in myocardial contractility acts to enhance stroke volume.

Permanent Artificial Cardiac Pacing

A defect in the conduction system of the heart may be treated by implanting a pacemaker unit. The early pacemakers of the 1960's provided an unsynchronized, fixed rate stimulus to the ventricles alone. Since then there have been many technological advances resulting in an increased reliability of the electrodes and corresponding complexity of pacemakers. Rate responsiveness, the ability of the pacemaker to increase pacing rate, was seen as an improvement over fixed rate pacing. In addition, synchronous pacing ensured that the contractions of the atria and ventricles occured in the natural sequence.

Pacemaker units are classified by a generic coding system (11,38) denoting the chamber that is paced, the chamber where sensing occurs and the response to sensing. The chamber coding may be A, the atria; V, the ventricle; or both, denoted D. The response to sensing may be inhibition, I; triggering of the pacemaker,T or either, D. Early pacemakers were VVI; they paced in the ventricle as well as sensing in the ventricle. If a natural ventricular stimulus was sensed the pacemaker was inhibited and did not provide a stimulus itself. As the ventricular rate was fixed increases in cardiac output could only be achieved through increases in stroke volume. Technological evolution has lead to the fully automatic or DDD pacemaker which can pace and sense in both chambers and respond by triggering a stimulus or by being inhibited. It is capable of operating in several different modes such as VVI, VDD, or

DVI.

Atrial synchronous pacing, VDD or VAT, is indicated when the individual has bidirectional complete heart block and a normal sinus node (22). Thus, the sinus rate can increase intrinsically with the pacemaker tracking the P wave and providing a stimulus to the ventricles. The timing interval between atrial contraction and ventricular stimulation is called the AV delay. This term in pacemakers is synonymous to the term PR interval. The normal components of increased cardiac output, heart rate and stroke volume are both utilized to meet metabolic demands in this type of pacing.

Rate Responsiveness

The normal physiological relationship is an increase in heart rate and stroke volume to meet the metabolic demands of exercise. Heart rate continues to increase toward maximum while stroke volume tends to plateau at a heart rate of approximately 120 beats·min^{-1} in the normal individual (1).

Many studies (11,18,20,32,35) have shown that the limitation of VVI pacing is the inability to increase the ventricular rate to match the metabolic demands of exercise. Thus, a proportionally large increase in stroke volume is required to increase cardiac output. Both maximal cardiac output and exercise tolerance are decreased as a result.

In separate studies, Kruse and Ryden (20) and Perrins et al (30) respectively observed a 20% and 27% increase in the

exercise workload with VDD versus VVI pacing. Kruse and Ryden (20) also measured the systolic time intervals of left ventricular ejection time (LVET) and pre-ejection period (PEP). In changing from VVI to VDD pacing at rest it was observed that the LVET index increased from 381 ± 25 msec. to 400 ± 22 msec., suggesting an increase in stroke volume.

Rossi et al (32) performed cardiac catheterization on 13 male and female subjects, 49-88 years of age, who had complete heart block with normal sinus node activity. Hemodynamic values were obtained during a Bruce treadmill test comparing VVI and VDD pacing. Subjects were subdivided into 2 groups with either normal (Group A) or decreased functional capacity (Group B). Resting stroke volumes were similar in all cases, while mean cardiac outputs were 4.66 ± 0.8 litres per minute ($l \cdot min^{-1}$) with VVI pacing and 5.45 ± 0.11 $l \cdot min^{-1}$ with VDD. Both groups showed much larger increases in stroke volume at maximum exercise with VVI pacing; 140 millilitres per beat ($ml \cdot beat^{-1}$) for Group A and 110 $ml \cdot beat^{-1}$ for Group B. Corresponding cardiac outputs were 10 and 7.5 $l \cdot min^{-1}$, heart rates were unreported. Due to the fixed rate with VVI pacing increases in cardiac output are only achieved by increases in stroke volume. VDD pacing resulted in stroke volumes of 80 and 85 $ml \cdot beat^{-1}$ at maximum for Groups A and B respectively; cardiac outputs were 12 and 10 $l \cdot min^{-1}$. The authors felt that the chronotropic response of VDD pacing allows for a moderate increase in stroke volume producing a greater maximum

cardiac output to meet exercise demands. Maximum workloads during the two pacing modes were significantly different in the normal group. In subjects with left ventricular dysfunction, maximum workload was 22% ($p<0.05$) higher during VDD pacing as compared to VVI, denoting the greater importance of rate responsiveness to this group.

Cardiac catheterization was also used by Karlof (18) to compare fixed rate ventricular (VVI) and atrial triggered (VAT) pacing. A total of 25 male and female subjects, 31-70 years of age, with complete AV block were divided into 2 groups. In Group 1 the VVI rate was maintained at 70 beats·min^{-1} while in Group 2 the VVI rate was matched to the exercise heart rate during VAT pacing. In Group 1 submaximal exercise stroke volume increased to 104 $\pm$ 14.8 ml·beat^{-1} for a mean cardiac output of 8.2 $\pm$ 0.9 l·min^{-1}. during VVI pacing at heart rates of 83 $\pm$ 15.4 beats·min^{-1}. For the same individuals stroke volume was 81 $\pm$ 15.5 ml·beat^{-1} and cardiac output 9.8 $\pm$ 1.6 l·min^{-1} at heart rates of 126 $\pm$ 11.5 beats·min^{-1} during VAT pacing. The proportionally higher stroke volumes are evident in VVI pacing where there is a lack of chronotropic response. In Group 2, the heart rates were matched at 121 $\pm$ 17.6 beats·min^{-1} for VVI and 122 $\pm$ 19.5 for VAT. Exercise stroke volumes were 72 $\pm$ 16.9 and 77 $\pm$ 21.8 ml·beat^{-1} respectively, producing cardiac outputs of 8.5 $\pm$ 1.6 and 9.2 $\pm$ 1.8 l·min^{-1}. Thus, despite matching heart rates, VAT pacing still produced a significantly ($p < 0.05$) greater increase in

cardiac output.

Synchrony of Atrioventricular Contraction

Normal ventricular filling initially occurs passively with blood flowing from the atria with the opening of the AV valves. An active filling phase occurs when the atria contract prior to ventricular systole. Assuming no change in afterload, this synchronized contraction sequence between the atria and ventricles enhances the preload or volume of blood entering the ventricles, thus increasing the end diastolic pressure and degree of myocardial fibre stretch. Following the Frank-Starling mechanism, stroke volume will be increased. In addition to increased ventricular filling, atrial systole assists in the closure of the AV valves. Without their closure, blood could regurgitate into the atria when the ventricles contract resulting in a decrease in effective stroke volume (5).

Braunwald (7) states that stroke volume is the result of the pumping abilities of the heart and the capabilities of the peripheral circulation to return blood to the heart. Specifically, increased contractility and preload are key determinants of increased stroke volume, with afterload having the effect of reduction. An appropriately timed atrial systole can increase preload. Further, the most effective mechanical activity of the left ventricle is gained through the optimal left ventricular end diastolic pressure. This can be achieved in two ways; maintaining a raised filling pressure throughout

diastole so that the ventricle is maximally filled just prior to systole or rapidly raising end diastolic pressure just prior to systole via atrial contraction (22). Unfortunately, the first method risks vascular congestion induced by high resting pressures.

The dynamic effect of atrial contraction upon ventricular response was studied by Brockman (6). Sixty-one mongrel dogs were instrumented with pressure transducers in the left heart and electromagnetic flowmeters on the aorta; forty animals had surgically induced complete heart block. During measurements in the animals with block atrial rates were 67-140 beats·min^{-1} while ventricular rates were 23-71 beats·min^{-1}. Various AV intervals resulted from the uncoordinated contractions. Maximum hemodynamic values were obtained when the spontaneous interval was in the range of 85-125 msec. Values were lessened at intervals that were either longer or shorter. With an interval in this optimal range a greater end diastolic pressure and fibre length were observed, resulting in a greater aortic pressure and stroke volume than obtained for the same animal with intervals outside the optimal. Generally, the end diastolic fibre length increased up to 40%, aortic pressure increased up to 25 mmHg and stroke volume increased up to 27 ml·beat^{-1} with intervals of 85-125 msec. versus those outside this range. These results in animals with complete heart block indicate the importance of the timing of atrial systole relative to ventricular systole. Data from the normal dogs was used to substantiate the responsibility

of atrial systole for the closure of the AV valves. There is an initial rise in atrial pressure with atrial contraction followed by a decrease in atrial pressure and an increase in ventricular pressure as the ventricle contracts. The authors felt it is this reversal in pressure gradient associated with a normal contraction sequence that closes the valves and prevents regurgitation of blood into the atrium.

Samet, Bernstein and Levine (34) studied 20 patients with complete heart block and a slow ventricular rate to illustrate the effect of atrial contraction in left heart dynamics of humans. Catheterization allowed the recording of pressures within the heart. They reported higher left ventricular diastolic pressures occurring when the P wave preceded the QRS complex by a normal interval than when the P wave was buried within the QRS. In one subject end diastolic pressure was 25-30 mmHg with normal sinus rhythm but only 11-17 mmHg during atrial fibrillation. During a run of premature ventricular contractions, end diastolic pressures were 23-30 mmHg when ventricular contraction was preceded by atrial contraction. At the same time, with ventricular ectopic beats, pressure reached only 13-16 mmHg. The authors felt the recording of peak end diastolic pressures with a normal temporal sequence between the P wave and QRS complex demonstrated the augmenting of ventricular filling by atrial systole.

Mitchell et al (28) performed experiments on dogs with induced heart block and instrumented with left heart pressure

transducers, flowmeters on the aorta and a pacemaker to control heart rate. These animals were paced in both the atrium and ventricle such that the pacing sequence could produce a ventricular contraction with or without a prior atrial contraction. The AV interval was set at 60-80 msec. These authors observed a drop in stroke volume at different heart rate levels when atrial contraction did not precede ventricular contraction. At rates of 60-90 beats·min^{-1} the mean decrease was 19% (range: 11-25%), at 120-150 beats·min^{-1} the drop in stroke volume was 24% (17-36%) and with rates of 180-210 beats·min^{-1} stroke volume decreased 34% (13-52%). Of interest is the higher decrement in stroke volume with higher heart rates perhaps indicating the greater impact of the loss of AV synchrony with increasing output demands. Another consideration is the need to adjust the temporal sequence between atrial and ventricular contraction rather than having a constant delay at all heart rate levels.

Abnormal hemodynamic effects of improperly timed atrial systole were reported by Skinner et al (37). Complete heart block dogs were instrumented for hemodynamic monitoring. Vagotomy and ganglionic blockage eliminated reflex compensation. Both the right atrium and ventricle were paced, therefore AV intervals were controlled. Ventricular rates were different for each animal but held constant throughout the measurements. The AV intervals of 60-120 msec. were found to produce the greatest aortic pressure, flow and left ventricular end diastolic

pressure. Intervals shorter than 50 msec. and longer than 200 msec. produced lower values. In addition, this optimal AV interval range resulted in lower mean left atrial pressure. Mitral regurgitation was observed in two animals utilizing a sensing electrode in the left atrium and absorbic acid injections into the left ventricle just prior to contraction. When the AV interval was outside the 60-120 msec. range absorbic acid was detected in the left atrium. With ventricular systole there was movement of blood from the ventricle into the atrium. Atrial asystole was induced in eight animals by withdrawing the pacing electrode. A decreased aortic pressure, flow and left ventricular end diastolic pressure resulted. It was also noted that atrial pressure increased in early ventricular systole, indicating regurgitation with the absense of atrial systole.

It appears that ventricular filling and preload as well as AV valve closure is augmented by a properly timed atrial contraction. Observation of the electrocardiogram relative to valve closure in the normal situation reinforces this concept. Onset of ventricular systole and valve closure coincide with the end of the QRS complex. AV valve reopening occurs after the T wave (5). If the AV interval is too short, the atrial contraction denoted by the P wave could occur against AV valves closed with the onset of ventricular systole. With inadequate time for atrial emptying, a portion of the atrial contribution to ventricular filling would be lost. If atrial contraction precedes the QRS by too long an interval, the atria will be

relaxed at the time of ventricular systole and blood could regurgitate through the AV valves. In other words, the pressure gradient observed by Brockman would not be maintained. If the AV interval is extremely long the P wave will start encroaching on the preceding T wave and atrial contraction could occur against valves still closed from the preceding ventricular contraction (22). Such a situation could occur as heart rate increases and the AV interval is not shortened.

The disrupted timing of the synchrony of AV contraction has a definate influence on hemodynamics of pacemaker patients. Karlof (18) studied the effect of AV synchrony on cardiac output by comparing fixed rate ventricular pacing (VVI) with atrial triggered pacing (VAT). Cardiac catheterization was performed on both male and female subjects with complete heart block, mean age 55 years, who were then studied at rest and during submaximal exercise during two series of tests performed in the recumbent position. During series I VVI pacing remained constant at 70 beats·min^{-1} while during series II the pacing rate was increased to match the heart rate of atrial triggered pacing. During exercise, VVI pacing at a fixed rate of 70 beats resulted in a proportionally larger increase in stroke volume to achieve an increase in cardiac output. Stroke volume was 104 $\pm$ 14.8 ml·min^{-1} at a heart rate of 83 $\pm$ 15.4 beats·min^{-1} for a cardiac output of 8.2 $\pm$ 0.9 l·min^{-1}. Atrial triggered pacing (VAT) allowed an increase in heart rate along with a moderate increase in stroke volume to produce a significantly

greater increase in cardiac output, stroke volume of 81 ± 15.5 $ml \cdot min^{-1}$ at a heart rate of 126 ± 11.5 $beats \cdot min^{-1}$ for a cardiac output of 9.8 ± 1.6 $l \cdot min^{-1}$; a response that closely resembles the normal physiological pattern. During series II, where heart rates were matched during rest and exercise, cardiac output was 18% higher at rest and 8% higher during exercise at the same workload with VAT pacing. Exercise stroke volumes were slightly, but not significantly, higher during VAT, 77 ± 21.8 $ml \cdot beat^{-1}$, than during rate matched VVI pacing, 72 ± 16.9 $ml \cdot beat^{-1}$. Cardiac output during VVI pacing was8.5 ± 1.6 $l \cdot min^{-1}$ while 9.2 ± 1.8 $l \cdot min^{-1}$ with VAT, a significant difference ($p<0.05$). It was felt that atrial triggered pacing offered the advantages of a greater increase in cardiac output during exercise due to the maintainence of AV synchrony and the ability to increase heart rate. Meanwhile resting stroke volumes were significantly higher with VAT pacing, 69± 16.2 versus 57 ± 14.9 $ml \cdot min^{-1}$ for VVI ($p<0.01$). This may indicate a greater effect of AV synchrony at rest than during exercise.

Pehrrson (29) assessed the physical work capacity of 14 subjects, aged 44 - 81 years, to analyse the importance of AV synchrony during exercise. Seven females and seven males with complete heart block were paced either VVI, VAT or VVI matched to the atrial rate but still asynchronous. On a bicycle ergometer they started at an initial power output of 10 watts, this was increased by 10 watts per minute until exhaustion. The

maximal exercise capacity in watts was 20% higher with VVI pacing when the atrial and ventricular rates were matched, maximal power output was 89 ± 28.3 watts at a ventricular rate of 72 ± 5.8 and an atrial rate of 139 ± 16.9 beats·min^{-1} during VVI compared to 107 ± 30.2 watts at a ventricular rate of 126 ± 12.6 and an atrial rate of 133 ± 12.3 beats·min^{-1} during VVI rate-matched. A further increase of only 4% was seen with VAT pasing; 111 ± 31.4 watts at a ventricular rate of 138 ± 12 and an atrial rate of 141 ± 13.1 beats·min^{-1} with an AV delay of 150 msec. Due to this minimal increase between VVI rate-matched and VAT pacing, the author felt that the ability to increase ventricular rate was a key factor in exercise tolerance rather than AV synchronization.

A study by Kristensson et al (19) supported this idea. Ten subjects with complete heart block treated with a VDD pacemaker had no other signs of myocardial disease as diagnosed by history, physical examination, ECG and chest X-ray. The 6 males and 4 females. age 20 -70 years performed a pre-test on a bicycle ergometer to establish their maximal steady-state workload. One week later, after cardiac catheterization, the subject rested for 30 minutes in a seated position whereupon resting values were obtained. With VDD pacing and an AV delay of 150 msec., the subject cycled at 50% and then 80% of their maximal steady-state power output for 7-8 minutes. Cardiovascular values were measured starting at the 4 1/2 minute mark of each stage. Following 2 hours of rest and reprogramming

to VVI pacing, the protocol was repeated with heart rates matched to those during VDD pacing. The results showed no significant differences in heart rates at all three levels. In addition, no significant differences were seen in stroke volume and cardiac output at the 50% and 80% levels. Stroke volume and cardiac output were significantly different ($p<0.05$) at rest; VVI rate matched was 64 $\pm$ 22 ml·beat^{-1} at a heart rate of 74 $\pm$ 14 beats·min^{-1} for a cardiac output of 4.5 l·min^{-1}, VDD stroke volume was 70 $\pm$ 19 ml·beat^{-1} at a heart rate of 74 $\pm$ 13 beats·min^{-1} for a cardiac output of 5.0 l·min^{-1}. It appears that AV synchrony keeps cardiac output higher at rest while with exercise it has a lesser importance. The authors attributed exercise improvement in VVI pacing to the renewed chronotrophic response with rate matching.

Greenberg et al (13) studied three modes of pacing to determine the influence of left ventricular filling pressure on the atrial contribution to cardiac output. Eighteen subjects with a mean age of 54 years (range 18-73 years) and various cardiac diseases were studied; 10 subjects were 24-48 hours post open heart surgery, 5 were assessed during cardiac catheterization and 3 were studied in an intensive care unit. All subjects were considered clinically stable and underwent cardiac catheterization for the study. Atrial pacing was used to establish baseline values. The pacing rate was approximately 10 beats above the individuals intrinsic rate and the mean PR interval was 220 msec. wiht intrinsic conduction. Subjects were

also paced ventircularly where both the atrium and the ventircle were stimulated simultaneously for an AV delay equal to zero. This would effectively remove the atrial contribution to ventricular filling. The third mode was AV sequential pacing with a mean AV delay of 130 msec. The atrial contribution was determined by subtracting the ventricular paced stroke volume from the atrial paced stroke volume.

Stroke volume index was an average of 25% higher with atrial pacing, 36.3 $ml \cdot m^2$ as compared to ventricular pacing, 29.0 $ml \cdot m^2$. Heart rate was the same at an average of 95.8 $beats \cdot min^{-1}$ with a mean pulmonary capillary wedge pressure of 19.7 mmHg for atrial and 22.9 for ventricular pacing. It was observed that as individual wedge pressures increased the calculated atrial contribution decreased ($r = -0.53$, $p<0.25$) and stroke volume was lower in patients with the higher wedge pressures. In subjects with wedge pressure $\leq$ 20 mmHg atrial contribution was 9.3 ± 1.3 $ml \cdot m^2$ compared to 2.4 ± 1.2 $ml \cdot m^2$ in subjects with wedge pressures $\geq$ 20 mmHg.

Pulmonary capillary wedge pressures were manipulated by volume loading subjects with normal left ventricular function and normal wedge pressure $\leq$ 20 mmHg. In one subject, wedge pressure was 19 mmHg and the atrial contribution calculated at 27%. After increasing pressure to 29 mmHg no difference between stroke volumes from atrial and ventricular pacing was noted; it was determined that the atrial contribution was ineffectual at this level.

The authors concluded that as filling pressure increases the atrial contribution to stroke volume is less. In addition, they felt subjects with left ventricular dysfunction benefit less from the atrial contribution than normal subjects when pulmonary capillary wedge pressures are greater than 20 mmHg. This could have implications for cardiac output during exercise.

Timing of the Atrioventricular Delay

A negative linear relationship has been demonstrated between heart rate and PR interval in normal subjects (9,36). In pacemakers the synonymous term for PR interval is AV delay. This delay can be programmed to various settings (25-250 msec.) in dual chambered pacemakers but remains at a constant despite changes in heart rate.

Haskell and French (15) studied 10 subjects with complete heart block treated with a dual chamber, DDD, pacemaker. The average age of the subjects was 50 years (range 26-78), half the group was female and the other half male. Doppler derived cardiac outputs were measured at rest in the supine postion. Three programmed rates of 80, 100 and 118 beats min^{-1} were assessed in combination with AV delays of 65, 100, 150, 200 and 250 msec. When compared to the baseline values at a delay of 65 msec., the highest mean cardiac output was seen with an AV delay of 150 msec. For any particular pacing rate, it was observed that the highest cardiac outputs were obtained at a delay of 150 or 200 msec. Outputs decreased at the same heart rate when the

AV delay was lengthened to 250 msec. or shortened to 100 or 65 msec. While the exercise situation was not addressed in this study, it appears that maximizing cardiac output at rest requires appropriate timing of the AV delay.

Bashour et al (4) used the non-invasive method of carotid pulse tracing to assess the relationship of systolic time intervals and AV delay in 7 patients with complete heart block. Resting LVET and PEP were measured from the combined use of ECG, carotid pulse tracing and phonocardiogram. These measurements are useful in that stroke volume is directly related to LVET and inversely related to PEP. At a heart rate of 70 $\pm$ 2 beats$\cdot$min^{-1} it was found that the maximum LVET corresponded to an AV delay of 200 msec., suggesting that the maximal stroke volume for this heart rate occured at this value. The LVET decreased with delays of less than 180 msec. or greater than 200 msec. In addition, PEP was minimal at delays of 180 and 200 msec.

The effects of various AV delays were studied by Leman and Kratz (21) via radionuclide evaluation. Ten subjects implanted with a dual chamber, DDD, pacemaker were assessed for left ventricular ejection fraction (LVEF), end diastolic volume (EDV) and stroke volume. The group contained both males and females with a mean age of 69 (range 54-86) years. During a bicycle ergometer test the pacemakers operated in the atrial tracking mode, VDD. In the heart rate range of 92-115 beats$\cdot$min^{-1} there was an increased EDV ratio and stroke volume ratio with an

AV delay of 100 msec. versus a delay of 150 msec. Thus, a larger stroke volume was produced with the shorter AV delay when heart rate was increased due to exercise.

In an unpublished project reported by Daubert et al (9), the hemodynamic effect of an AV delay adapting to the pacing rate was compared to fixed delays of 150 and 200 msec. Pacing rate was increased from 90 beats·min^{-1} with an AV delay of 200 msec. to 150 beats·min^{-1} with a delay of 100 msec. every 5 minutes while the subject was at rest. The authors report that the best hemodynamics were found with the adaptable AV delay. They state significant differences in cardiac index, wedge pressure, left ventricular stroke work index and systemic vascular resistance existed between the adaptable and fixed AV delays. The greatest effect occurred at the higher heart rates of 130, 140 and 150 beats·min^{-1}.

Mehta et al (25) used continuous wave Doppler to measure cardiac output in 8 subjects of mean age 53 years (range 22-71) implanted with DDD pacemakers. All had normal left ventricular function and were paced at 70, 90 and 100 beats·min^{-1} with AV delays of 75, 100-110, 140-150 and 200 msec. The studies were done at rest. Their results showed that cardiac output was significantly greater at a heart rate of 100 when the AV delay was 100 msec. as compared to 200 msec. At heart rates of 70 and 90 beats·min^{-1} cardiac output was maximal at an AV delay of 150 msec. Ths authors felt that shorter AV delays may be beneficial in physically active subjects who require a faster

pacing rate.

Ritter et al (31) compared fixed AV delays of 200 and 150 msec. to a rate adapting delay in 10 subjects with DDD pacemakers. Measurements were made during cardiac catheterization in a resting supine position. Pacing rates of 90 to 150 beats·min^{-1} were assessed. The authors reported significant differences between the rate adapting and fixed AV delays in pulmonary capillary wedge pressure, cardiac index, left ventricular stroke work index and systemic vascular resistance. The most favourable hemodynamic efficiency was obtained for the adapting delay especially for rates of 120, 130 and 140 beats·min^{-1}.

It must be emphasized that the above three studies were performed at rest without the increased venous return to the heart produced by exercise.

In another study, Mehta et al (26) evaluated the optimal AV delay with exercise in patients with normal ventricular function. Doppler measurements were made during the last 15 sec. of treadmill exercise corresponding to Stage 1 of the Bruce protocol. Nine subjects with a mean age of 53 years (range 22-70) and pacemakers programmed to the DDD mode were assessed for cardiac output during four separate tests. AV delay was programmed to either 75, 100, 150 or 200 msec. Heart rate at peak exercise was similar for all tests, approximately 102 beats·min^{-1}. The cardiac output was greatest for the shortest AV delay, 8.26 $\pm$ 1.1 l·min^{-1} at 75 msec. At 150

and 200 msec. the cardiac output was 7.46 ± 0.9 and 7.85 ± 1.1 $l \cdot min^{-1}$ respectively, significantly different ($p<0.05$) from the shorter AV delay. While the resting cardiac output was greatest for an AV delay of 150 msec. at 5.81 ± 1.5 $l \cdot min^{-1}$, the 75 msec. delay produced the lowest, 5.20 ± 1.3 $l \cdot min^{-1}$. The authors concluded that a rate adapting AV delay could improve the hemodynamic response to exercise and thus, exercise tolerance in patients with dual chambered pacemakers.

Oxygen uptake, anaerobic threshold and lactate levels were examined by Haskell and French (16) in 7 subjects aged 51 ± 14 years with dual chambered pacemakers. The subjects had intrinsic sinus rhythm therefore were paced in the VDD mode; three had dilated left ventricles and four showed signs of decreased left ventricular function with echocardiography. A long AV delay of 168 ± 12 msec. was compared to a shorter delay of 66 ± 4 msec. during maximal bicycle exercise testing. There was no significant differences in cardiopulmonary indices nor exercise duration for the two delays. Maximal work rate was similar; 61 ± 36 watts for the short delay and 64 ± 38 watts for the long delay. Maximal oxygen uptake was 15.7 ± 2.6 for the short delay and 15.6 ± 2.8 $ml \cdot kg^{-1} \cdot min^{-1}$ for the long delay. Maximal heart rates were similar at 123 ± 26 and 128 ± 28 $beats \cdot min^{-1}$ for the short and long delays respectively. It was felt that during exercise in this group of patients the shorter AV delay did not provide any improvement in cardiopulmonary function.

Maximal exercise capacity was assessed by Ryden et al (33) to determine the influence of various AV delays. Fifteen subjects (52-76 years) with complete heart block treated with VDD pacing performed 5 bicycle ergometer tests. A ramp loading protocol was followed to produce a symptom limited maximum in less than 10 minutes. AV delays of 50, 100, 150 and 200 msec. were programed for each of 4 different tests with the fifth test consisting of asynchronous ventricular pacing. Results showed no significant differences between maximal exercise capacity measured in watts, peak VO_2 and ratings of perceived exertion. Heart rates at maximum were not significantly different for the 4 AV delays. Asynchronous pacing produced a lower heart rate than delays of 50 and 100 msec. without influencing exercise capacity. These authors concluded that proper timing of the atrial contribution decreases in importance with exercise as indicated by no significant differences in maximal exercise capacity and VO_2 at various AV delays. Restoration of the ability to increase heart rate was deemed the most significant factor.

At present, the AV delay of a pacemaker is fixed at some interval and does not change with increasing heart rate. It may be that in order to permit a more normal physiological response to exercise in individuals with dual chambered pacemakers the AV delay must shorten with increasing heart rate following the pattern seen in the normal relationship.

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